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Dualism of the Aging Process

Yoga and Botulinum Toxin Reduce

Highlights

Clinical and Metabolic Disorders

Self-Care for Arteriovenous Fistula

Discovering Thoughts, Inventing Future

VOLUME 25 ISSUE 3 VERSION 1.0

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Yoga and Botulinum Toxin Reduce Adolescent Idiopathic Lumbar Scoliosis – A Control, Randomized Study

By Loren Fishman & Bernard Rosner

MD Columbia University Medical School

Abstract- *Background:* Approximately 90% of scoliosis is adolescentidiopathic (AIS). From 10–14 years of age until 20, the spine is most vulnerable. An effective non-surgical means of remediation is welcome.

Design: Randomized, controlled, three-arm study assessing safety and efficacy of yoga with incobotulinum injections to reverse lumbar and thoracolumbar AIS.

Methods: Private clinic setting. Non-pregnant, healthy 12–20-year-olds with AIS performed either a "placebo" yoga pose (Group 1), the side plank (Vasisthasana) with placebo injection (Group 2) or side plank with incobotulinum injections (Group 3). In Group 3, 33 IU of incobotulinumtoxin were injected into the concave-side lumbar paraspinals, quadratus lumborum at curve's apex, and psoas with needle entry at L3–4; Group 2 received equal volumes of normal saline solution at the same locations. Random.org provided randomization.

Keywords: *adolescent idiopathic scoliosis, botulinum toxin, yoga.*

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Yoga and Botulinum Toxin Reduce Adolescent Idiopathic Lumbar Scoliosis – A Control, Randomized Study

Loren Fishman [α] & Bernard Rosner [σ]

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Objective: Determine safety and efficacy of increasing muscular strength symmetry in AIS.

Results: Each group had 10 patients. All completed the three-month study period. Mean self-reported daily side plank time = 155 s. The mean initial lumbar curvatures for groups 1, 2 and 3 were 29.8, (SD 6.6), 37.8 (SD 8.0) and 33.0 (SD 6.31) degrees, respectively. Curves were reduced at 3 months by +1.8 (2.4), -7.8° (7.1) and -12.2°(8.79) respectively, with ($p < 0.001$) improvement in Group 2 vs. Group 1 and Group 3 vs. Group 1. Group 3 showed the greatest improvement. Harms: one patient in Group 2, one in Group 3, with transient shoulder pain that resolved by using the forearm in the pose.

Conclusion: Muscle strength asymmetry appears to be relevant to AIS treatment. Side planks performed with the convex side downward alone and side planks combined with incobotulinum injections on the concave side appeared more effective in reversing lumbar AIS than placebo exercises. Incobotulinum injections with yoga appeared to be the most effective.

Keywords: adolescent idiopathic scoliosis, botulinum toxin, yoga.

This study was conducted in accordance with the Declaration of Helsinki and approved by the institutional Review Board CIRBI, now Advarra on December 2, 2020.

Author α: MD Columbia University Medical School.
e-mail: loren@sciatica.org
Author σ: Ph.D. Harvard University Biostatistics.

This study was conducted in accordance with the Declaration of Helsinki and approved by the institutional Review Board CIRBI of Advarra on December 2, 2020.
It was registered at ClinicalTrials.org at NCT04922983 on 17 July 2021.
Neither Dr. Fishman nor Dr. Rosner have conflicts of interest regarding this paper.
The data for this study can be found on Figshare.

I. Introduction

Scoliosis is a three-dimensional spinal curve with side-to-side curve(s) and spinal rotation. It affects 2 - 3% of the world's population.[1] Of Earth's approximately 8 billion people, 160 – 240 million people suffer from scoliosis. Effective antibiotics for tuberculosis and vaccines for polio have made adolescent idiopathic scoliosis (AIS) nearly 90% of all scoliosis[2] Females are more likely than males to acquire the condition, the ratio changing from 1.4:1 in curves of 10–20 degrees to 7.2:1 in curves above 40 degrees.[2] Although asymmetric sports such as tennis and baseball have no bearing on scoliosis, dancing significantly raises the risk.[3] It is uncertain whether this is due to ligamentous and bone changes or to the greater flexibility of dancers, enabling asymmetric forces to curve the spine more readily.

When a curve's Cobb angle exceeds 25 degrees, braces are often implemented to deter progression, since this is the level at which most studies report the highest rates of progression.[4-7] However, several other systems make their own determinations: The Rigo–Cheneau classification stipulates its own guidelines for implementation, and designs and crafts braces in ways that may depart somewhat from the 25-degree demarcation.[8] It coordinates brace design with fabrication, using its own principles of correction, and thus has control over the relationship between when to prescribe and what is furnished. The soft Spine-Cor brace has its own system as well, with its own parameters of internal consistency.[9]

Generally, braces are not expected to diminish curvature but rather reduce curve progression.[10] Nevertheless, the Spine-Cor and Lyons braces have been reported to have corrective capacities.[11,12] When the goals of bracing were polled among authorities in the field, aesthetics, quality of life, disability, back pain and psychological well-being were found to be the most important goals in that order.[13] These goals are promoted naturally through curve correction as well. The same group judged the evidence in favor of bracing to be stronger than the evidence for any other conservative modality, with scoliosis-specific exercises second.[14] Nevertheless, discomfort, embarrassment at school, lowered self-esteem, body image[14] and consequent issues of compliance are relevant, and questions have

been raised about whether core stabilization, scoliosis-specific exercises, and even the use of a second orthotic or insoles improve braces' efficacy.[13,15]

Other conservative methods, such as the Schroth, and chiropractic systems, such as Pettibone and Clear, have mixed reports regarding efficacy, and physical therapeutic exercise programs are also currently being tested.[16-19] Greater clarity on ancillary treatments with braces is desirable, especially concerning the underlying principles that can guide therapeutic decisions.

Typically, surgical intervention is considered only when curves exceed 45 degrees. Surgery has rightfully dominated the field of scoliosis since it has been the most reliable and effective remediation for many years. The natural history of AIS suggests 0.4 to 2.2 degrees of annual progression, depending upon age, Risser number and curve type, although teenagers' spines are capable of much greater change.[4-6] When visiting their surgeons, young patients have an X-ray taken, and they and their families often are told of the 45-degree threshold for surgery. With or without braces, parents and their children with AIS are relegated to the passive role of "watchful waiting" unless and until curves reach 45 degrees.

Although genetic, anatomical and neuroanatomical correlates of AIS have been discovered[20-23] promising physiotherapeutic work to effectively stabilize and reverse scoliosis awaits high-quality studies that confirm it.[24] A reliable, innocuous method would be particularly valuable since, unlike major surgery, it could be instituted in patients with much smaller curves, when treatment would commence earlier and likely would not be as disruptive nor last as long.

Previous work suggests electrophysiological and hormonal muscular asymmetries are at work in AIS,[25,26] supporting the possibility that muscular imbalance may be a relevant factor in its pathogenesis. We tested this hypothesis by utilizing botulinum toxin type A, incobotulinum, a medication that temporarily weakens muscles, on the concave side of lumbar curves, and an asymmetrical yoga pose, the side plank, to strengthen the convex side. Incobotulinum has few other effects after intramuscular injection.

The hypothesis that muscular imbalance is important in AIS is also supported by a study finding that the Schroth method, a muscle-oriented treatment, significantly improved curves.[19] Further, this single yoga pose, the side plank, performed with the convex side of lumbar curves held inferiorly, was found to be helpful in lumbar AIS in multiple studies.[27-29] A randomized, controlled repeat of this method found it ineffective,[30] but close reading of that study reveals that unfortunately, the randomization of the intervention group was such that not a single patient with a lumbar curve was included in it.[31] In the current study, we used the side plank to strengthen the weaker (convex) side and added incobotulinum injections of the contralateral (concave) paraspinal, quadratus lumborum and psoas muscles to temporarily weaken the stronger side. Bracing of patients was not permitted during the test period to avoid a confounding factor. Testing the validity of the muscular imbalance hypothesis, the primary and secondary objectives of this study were to assess the benefits and the harms[32] of combining incobotulinum injections with yoga to reverse lumbar and thoracolumbar AIS.[28-30]

The current study has been approved by the Chesapeake IRB (now Advarra) and the FDA, since this use of botulinum toxin is virtually new in the United States. One other institution is studying it in a similar context.[33] The current study was made public on Clinical Trials.org NCT04922983 on 17 July 2021 and was accessed on that day. Recruitment began 17 July 2021.

II. Methods

This is a randomized, controlled study, with two non-botulinum groups: Group 1 received a placebo yoga pose only, while Group 2 received the intervention yoga pose and preservative-free normal saline (placebo) injections. The full intervention group, Group 3 received both the interventional yoga pose and botulinum injections.

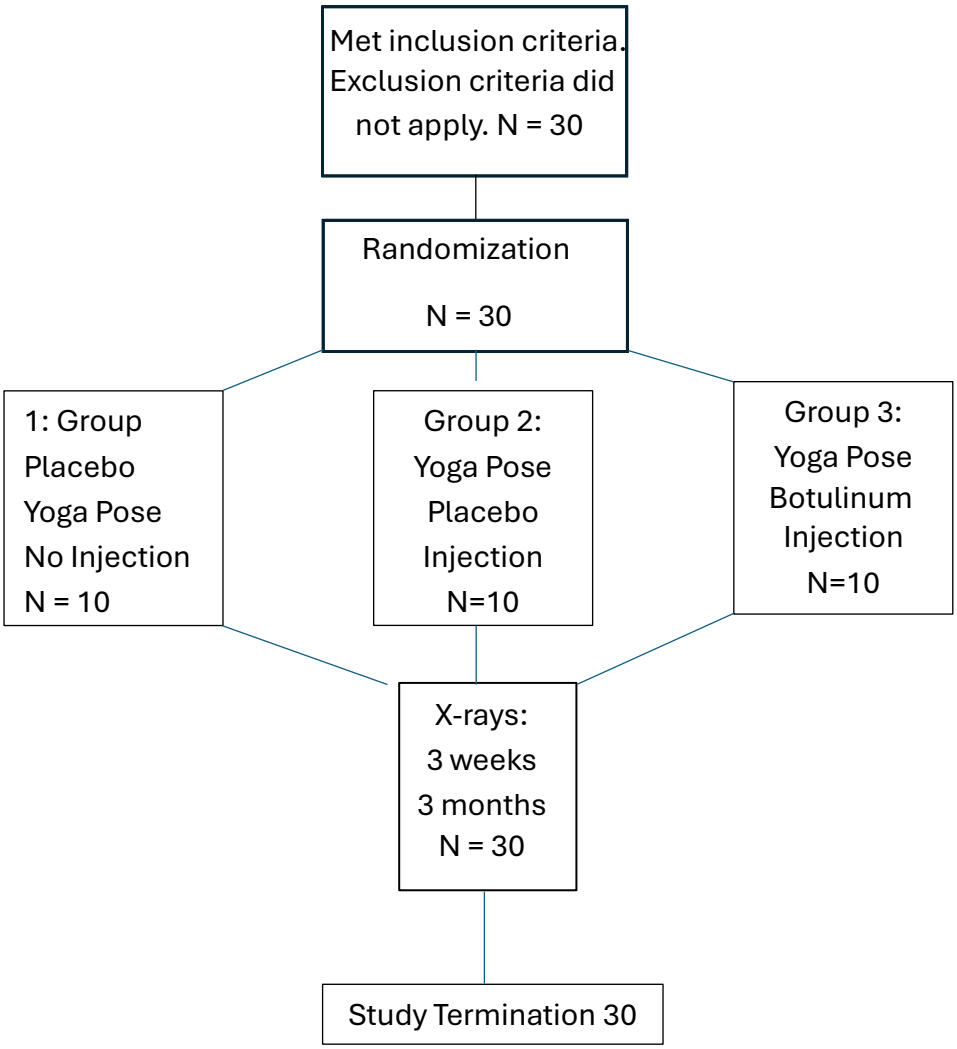

Figure 1: Flow Chart

a) Eligibility

i. *Inclusion Criteria*

- Age 12–20 years.
- Lumbar or thoracolumbar curve of 25°- 45°.
- Willingness to perform one yoga pose for as long as possible three times daily for three months.
- Parental or guardian agreement.

ii. *Exclusion Criteria*

- Neuromuscular or musculoskeletal disease, e.g., cerebral palsy, Guillain–Barre syndrome, Marfan's syndrome.
- Current use of brace.
- Previous spinal surgery.
- Previous exposure to botulinum toxin type A.
- Positive pregnancy test.

iii. *Particulars of the Study*

The study was conducted in private offices in Manhattan, New York, USA.

The study accepted non-pregnant applicants who had 25°-45° lumbar or thoracolumbar curves on Cobb X-rays completed less than 6 months before their visits. Group 1 patients were given a regular yoga pose, the plank, that consists of a symmetrical two-handed suspension of the upper body with extended elbows and lower body suspended on dorsiflexed feet. Group 2 patients were given the side-plank (*Vasisthasana)* in which the body is supported by one extended arm with the torso's coronal plane perpendicular to the floor and the lower body weight supported by the posterolateral foot of the convex side of the curve, and placebo injection of 0.33 cc normal saline injected into each muscle: the lumbar paraspinals opposite the apex of the curve, the quadratus lumborum opposite L3, and the psoas with needle entry approximately 7 cm. lateral to the L4 spinous process. Group 3 patients were given the side plank and injections of 33 IU incobotulinum into these same muscles. All injections were given on the curves' concave sides. Paraspinal and quadratus lumborum injections were performed with 1.5 inch inoject needles; the psoas injection was performed with

a 7 inch inoject needle; all injections were conducted under EMG guidance. Instructions to both placebo and interventional participants were that poses were to be performed three times daily for as long as possible each time. Patients' vital signs and weight were tested before the injections and again (except for weight) 15 min after the injections. Patients repeated their scoliosis X-rays at 3 weeks and 3 months. EOS technology was used whenever possible to minimize exposure to radiation. Checks on participants' compliance with the three-times-daily full plank or side plank regimen were made by telephone and email.

Power calculations based on previous papers[23-25] yielded 10 subjects in the control group and ten subjects in the study group, where alpha = 0.05 and (1 – beta) = 80%, (10 subjects per group). Statistical measures included regression analyses, both crude and adjusted for age, weight, Risser score, and sex. Randomization was conducted through random.org as patients qualified for the study presented in the office. There was no blocking.

Each patient or the parents of patients under 18 read and signed the Informed Consent Form. A medical assistant enrolled the patients; the office manager generated the randomized treatment group. The medical assistant prepared the syringe with preservative-free normal saline or lyophilized incobotulinum plus 1 cc of preservative-free normal saline, both colorless liquids. The participants, care providers and radiologists performing the initial and subsequent scoliosis X-rays and measuring Cobb angles were all blinded regarding group assignment. Apart from Group 1, which performed the two-handed 'placebo' yoga pose, and which of necessity was different in appearance from the intervention yoga pose, and the fact that this group had no injection, all procedures were indistinguishable to participants, care givers and radiologists. Mixed effects regression analyses were used to test the hypotheses, since differences between three groups was sought.

This study was conducted in accordance with the Declaration of Helsinki and approved by the institutional Review Board CIRBI of Advarra on December 2, 2020.

It was registered at ClinicalTrials.org at NCT04922983on 17 July 2021.

III. Results

Groups 1 and 2 made up control groups of 10 patients each, with 3 males in each group. Group 3 had 10 patients with one male. (See figure 1.) Mean age of controls and intervention patients: Group 1: 16.2 (S.D. 2.5); Group 2: 16.8 (2.8); Group 3: 15.8 (2.0). Mean weight of controls and intervention groups: Group 1: 119.3 lb. (10.7); Group 2: 117.5 lb. (20.2); Group 3: 126.7 lb. (13.0). Risser numbers: Group 1: 3.96 (.9) Group 2: 3.6 (1.4) Group 3: 3.7 (.7)

Table 1: Demographics

Group	Age	Male	Wt	Side	Size	Type	R#	FHx
Group 1	16.22	3	119.33	6 Rt	29.8	4S,2L,4TL	3.96	**50%**
SD	2.49		10.7		6.89		0.93	
Group 2	16.8	3	117.5	3 Rt	38.1	5S,2L,3TL	3.6	60%
SD	2.80		20.17		7.97		1.4	
Group 3	15.8	1	120.1	2 Rt	33	3S,3L,4TL	3.8	50%
SD	2.00		20.17		6.31		0.73	
Mean	15.1		119.0	3.7 Rt	33.63	2.6S,4.3 L,4TL	3.7	53%

Wt = weight.
Side = curve side.
Size =Cobb angle of lumbar or thoracolumbar curve.
Type =Curve type: S = "S" or "Inverted S" curve, L = lumbar, TL = thoracolumbar.
R# = Risser number.
FHx = Positive family history

Group 1 had 1 dropout, with two dropouts in both Groups 2 and 3 that were non-compliant at second or third X-rays. Three prospective patients experienced injection anxiety after randomization but before any treatment was initiated and therefore were not treated or included in the study. There were no reported injuries from the yoga pose in any group beyond a few days of sore shoulder and forearm muscles: one patient in Group 2 and one in Group 3 had transient complaints of this nature. These two patients continued the side planks on their forearms, but they did not otherwise alter their yoga routines. There were no changes in vital signs or later side-effects after administration of incobotulinum or placebo.

With rarely missed days, all patients reported performing the side plank or full plank at least twice daily beginning at a mean 30 s per side plank, with a mean initial cumulative reported dose of 80 s daily and ending at a mean 73 s per side plank after 3 months, with a mean cumulative dose of 160 s daily, during the three-

month period. Most participants performed the multiple side planks successively in the morning.

Mean lumbar scoliosis at study onset: Group1:29.8° (S.D. 6.68), range:25°-45°;Group 2: 38.1° (S.D. 6.52), range: 25°-45°; Group 3: 33.2° (S. D. 6.7), range: 25°-45°. Mean 3-week Cobb measurements were Group 1: 30.15°(S.D. 6.73.); Group 2: 29.4° (S.D. 9.19); Group 3: 24.0° (S.D. 8.3). The three groups were roughly equivalent at study onset. (See table 2.) Cobb measurements at 3 months were Group 1: 31.6° (S.D. 7.08); Group 2: 30.35° (S.D. 11.52) and Group 3: 21.0(S.D. 8.3).

Significant differences appeared between Groups 1 and 3 at three weeks ($p < 0.001$) and at 3 months ($p < 0.001$); between Groups 1 and 2 at 3 weeks ($p < 0.001$) and 3 months ($p < 0.001$). Group 3 was clinically significantly improved vs. Group 2 at 3 months (p = .056). (See tables 2 and 3 and figures2, 3 and 4.)

Table 2: Study Results

	Group					
	1		2		3	
	(N = 10)		(N = 10)		(N = 10)	
Variable	mean	sd	mean	sd	mean	sd
Age (yrs)	16.0	2.4	16.8	2.8	15.8	2.0
Weight (lbs)	119.3	13.7	117.5	20.2	126.7	13.0
Risser	3.9	0.9	3.6	1.3	3.7	0.7
Male sex (%)	0.30		0.30		0.10	
Score_T1	29.8	6.6	37.5	8.0	33.2	6.7
Score_T2	30.2	6.2	28.8	10.2	24.0	8.3
Score_T3	31.6	6.4	29.8	12.7	21.0	9.2
Change Score T2 minus T1	0.4	1.6	-9.1	5.8	-9.2	5.8
Change Score T3 minus T1	1.8	2.5	-7.8	7.3	-12.2	5.2

Table 2: sd = Standard deviation.
T1 = Cobb angle at study onset.
T2 = Cobb angle 3 weeks after study onset.
T3 = Cobb angle 3 months after study onset.

Table 3: Regression Results

Time Points		Comparison of Group 2 vs. Group 1			Comparison of Group 3 vs. Group 1			Comparison of Group 3 vs. Group 2		
		Beta	se	p-value	Beta	se	p-value	Beta	se	p-value
T2 minus T1	Crude	-9.1	2.2	< 0.001	-9.6	2.2	< 0.001	-0.4	2.0	0.85
	Adjusted[a]	-0.3	2.5	0.001	-9.9	2.5	< 0.001	-0.6	2.7	0.83
T3 minus T1	Crude	-9.6	2.4	< 0.001	-14.0	2.4	< 0.001	-4.5	2.4	0.076
	Adjusted[a]	-9.4	2.7	0.002	-15.1	2.6	< 0.001	-5.7	2.8	0.056

[a] *Adjusted for age, weight, Risser score, and sex.*
Table 3: se = Standard error.
T1 = Cobb angle at study onset.
T2 = Cobb angle 3 weeks after study onset.
T3 = Cobb angle 3 months after study onset.

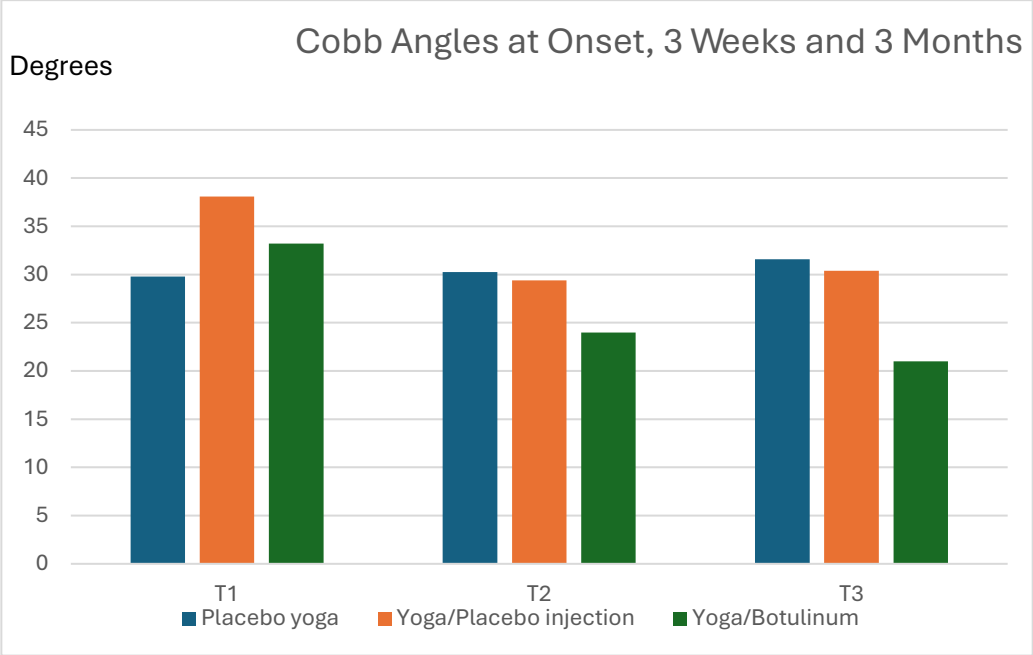

Figure 2: Greatest Reductions with Yoga and Botulinum

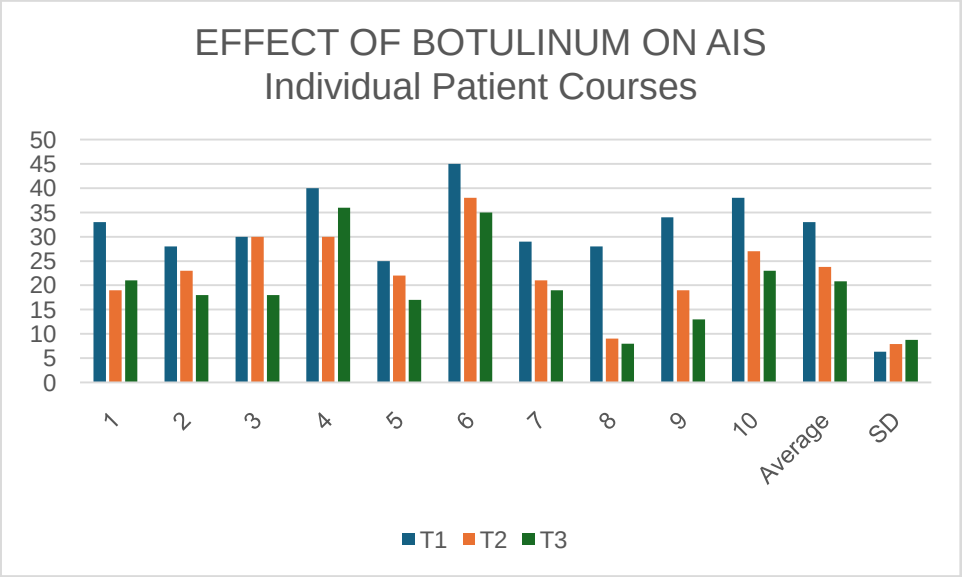

Figure 3: T1 = Study onset T2 = 3 weeks later. T3 = 3 months later. The magnitude of individual curve improvement: Group 1 (left-most columns) placebo yoga, Group 2 (middle column) true yoga pose and placebo injection, and Group 3 (right-most columns) true yoga pose and botulinum injection into the concave side's paraspinal musculature, the quadratus lumborum and the psoas muscles

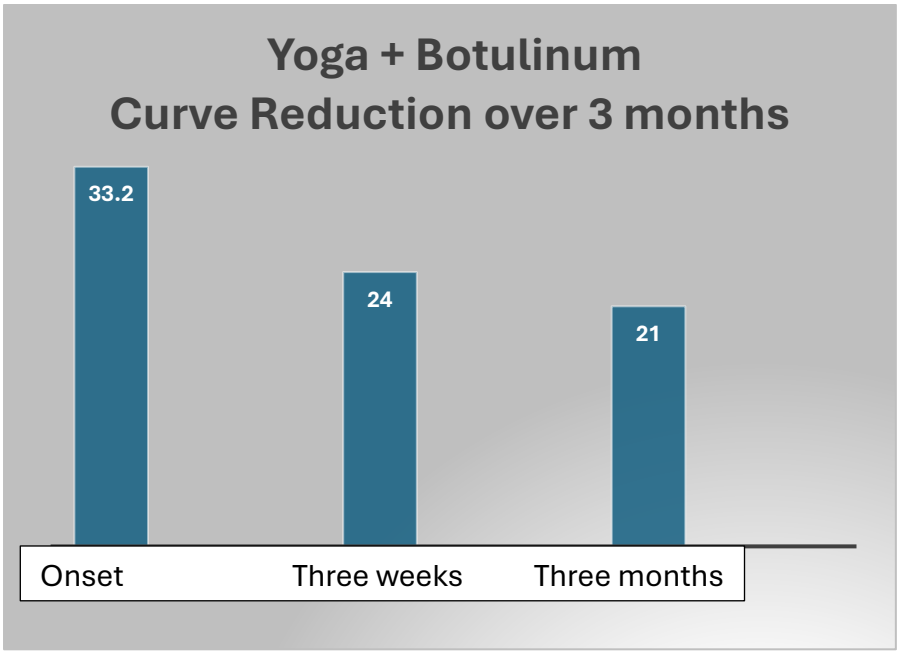

Figure 4: Mean curve reduction in Group 3 over 3 months = 36.75%

Apart from the transiently sore shoulders and forearms mentioned above, no harms were seen in any participants, although they were rigorously sought along SOSORT guidelines.[13]

IV. Discussion

The data, results and implications of this small study must be regarded with caution.[32] We view the spine as a tensegrity structure, a concept of the architect Buckminister Fuller which embraces configurations known for their strength and dynamic response to load,[34] like the human spine. Tensegrity structures are not held together by nails or rivets but by tension between their parts. Tent poles, Roman arches and radio antennae with their supporting cables are examples. The solar system, and the Bohr atom are somewhat extended examples, with gravity and centrifugal force, and electrical charges force providing the invisible tethers that generate tension and retain the structures' integrity. The spine may be seen as such a structure, but unlike the static edifices of architecture, the spine is held together by the quite variable tensions of the muscles that surround it. A spine-like tower by Frei Otto, *Vertebras Tensadas,* which curves in response to pressure from its cables is an architectural example of this. Seen this way, pervasive muscular asymmetry could be a major aspect of scoliosis.

Throughout the phylum *Chordata*, the spinal cord and the notochord are composed of many segments or metameres. These elementary units are interrelated in their control and in their movements and comprise a basic defining characteristic of the phylum. The spinal cord and its attendant ligaments, and, critically, its muscular attachments, always allow for movement and changes in leverage in all three planes, although this differs greatly from, e.g., thoracic to lumbar spine. In the turtle, it is the ribs that have coalesced to form the shell; inside it is a segmented creature with a flexible spine. To the authors' knowledge, in no case does a single bone form the spine the way the femur forms the sole support in the thigh. Throughout the phylum, from reptiles to humankind, the spine is always firm, but flexible in its multiple vertebrae,giving support, balance and leverage to our various bending, twisting, liftings and inclinations. However, many of the prominent surgeries of our day fuse the spine, rendering portions of it inelastic in a way nature has never allowed. An alternative therapy that repairs the spine without fixing it in a set conformation would be advantageous.

Significant improvement in Cobb angles at three weeks post-botulinum-injection in Groups 2 and 3 vs. Group 1 supports the hypothesis that some AIS is due at least in part to muscular imbalance, and that efforts to strengthen the convex muscles and temporarily weaken the concave muscles reverse the scoliosis significantly. Previous work with children with cerebral palsy had been ineffective and possibly dangerous,[25] but EMG work with children having AIS reveals that botulinum toxin alters side-to-side muscle recruitment ratios.[36] The simultaneous use of yoga and incobotulinum seems to have several advantages even after the two-month period of the medicine's activity:

1) Although inactive after two months, longer-term reduction in muscle tension is seen in botulinum toxin's cosmetic and dental uses.[37-41]

2) The botulinum weakens the strong (concave) side of the lumbar curve, enabling the actin and myosin fibers of the weak (convex) side to slide further together, increasing the number of cross bridges, and proportionately increasing their power to contract.[42]
3) Three-times-daily practice of the side plank yoga pose alone, held for as long as possible once daily, has been shown[27-29] to reverse lumbar curves due to AIS, through its strengthening effect on muscles of the convex side of the lumbar curve during the three-month period. The "head start" given by the incobotulinummay raise patients' enthusiasm, a critical ingredient in maximal compliance.

The adolescent idiopathic scoliotic spine is vulnerable to severe deepening of its curve. This is evidenced in the dramatic increase in Cobb angles seen in some patients. This may suggest that the actual advantage of the incobotulinum-plus-side-plank program may be even greater than those seen in this study of adolescents. This tendency of AIS to worsen dramatically in the teen years may to some extent obscure the actual benefit that intervention group patients received regarding the corrective influence of the yoga plus botulinum injections.

If the efficacy of this method is borne out in larger studies, it is sufficiently innocuous, low-cost and readily available to enable young people and their parents to embark on treatment of lumbar and thoracolumbar AIS as it develops, and before it reaches anatomically and socially significant levels.

V. Limitations of the Study

1) Although it reached statistical significance, this randomized controlled study is based on a small sample. Larger, randomized controlled trials are clearly necessary to demonstrate the efficacy of the botulinum-plus-yoga treatment more reliably.
2) A single blinded radiological opinion was utilized throughout this study. A second and even a third blinded radiologist (for non-unanimous assessments) would improve the objectivity in these studies.
3) The opposite limitation is also present: the ranges of the patients' Risser numbers, ages and curve sizes are too large. Some researchers find that a combination of bracing and exercise is differentially effective in AIS at different Risser numbers and this type of variability may apply to the current study's treatment as well[4-6] and should be investigated.
4) Studies have found that bracing plus exercise substantially improve curves in AIS.[43] Studies using bracing and exercise, including the side plank and botulinum toxin injections, might further advance and enhance conservative treatment.
5) Further study design can also raise the level of objectivity regarding harms, e.g., by measuring activities of daily living.[44] More specific considerations mentioned by leaders in the field may also be relevant, including aesthetics, quality of life, disability, back pain, psychological well-being, self-esteem, body image and embarrassment in high school.[13,14]
6) Longer follow-up is also necessary to demonstrate the value of the treatment. Two- or three-year follow-up or more would be desirable.
7) This study injected the minimal effective doses of botulinum. Dosages up to six times greater are patently safe.[45] It is possible that a proportionately greater effect would be seen with larger doses of incobotulinum. This study does not answer that important question.
8) One may additionally question whether the most relevant muscles have been treated. The iliocostalis, longissimus, semispinalis and spinalis muscles, as well as the external and internal intercostals and obliques, the superior and inferior serratus posterior, the subcostal, the quadratus lumborum, the latissimus dorsi and trapezius, the transversus abdominis, the rectus abdominis and the diaphragm itself might all function to laterally flex and/or rotate the spine. These muscles should be studied, both with EMG and possibly musculoskeletal ultrasound in different exercises and other types of exertion vis à vis strengthening them, and for appropriate dosages of botulinum toxin to weaken their contralateral counterparts.

VI. Conclusions

Muscular imbalance appears to play a part in the pathogenesis and longevity of adolescent idiopathic lumbar scoliosis. The side plank and botulinum toxin type A injections may be more effective in reversing lumbar AIS than a placebo yoga pose.

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Institutional Review Board Statement

This study was conducted in accordance with the Declaration of Helsinki and approved by the institutional Review Board CIRBI, currently Advarra on December 2, 2020, approval number "The IRB approved the above referenced protocol and the site with the modifications listed below on 28 May 2021: Modifications to the Adult/Parent/Subjects turning Age of Majority (AOM) Informed Consent Form".

Informed Consent Statement

Written informed consent was obtained from all subjects involved in this study. In the case of minors, written informed consent was obtained from their parents or guardians.

Data Availability Statement

The data for this study can be found at Figshare.

Conflicts of Interest

The authors affirms that they have no conflicts of interest with the subject-matter or any part of the paper given above.

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Stillbirths and Neonatal Deaths in Conflict Zones: A 10 Year Review of Health System Disruption and Collapse

By Dr. Firi. L. Promise & Dr. Peculiar Ihunwo

Abstract- Armed conflict significantly increases the risk of stillbirths and neonatal deaths, particularly in low and middle income countries (LMICs) where health systems are fragile or in active collapse. Over the past decade, countries such as Syria, Yemen, South Sudan, and Ukraine have experienced substantial deterioration in maternal and neonatal outcomes due to both direct and indirect effects of conflict. This paper employs a narrative synthesis of published and grey literature to assess the burden of perinatal mortality in conflict zones, with particular attention to trends in stillbirth and neonatal mortality, disruptions in service delivery, and the responses of global health actors such as UNICEF, the World Health Organization, and Médecins Sans Frontières. In several conflict-affected regions, stillbirth rates have reached forty per one thousand births, while neonatal mortality exceeds fifty per one thousand live births more than double the global average.

Keywords: stillbirths, neonatal mortality, conflict-affected settings, maternal health, humanitarian response, perinatal outcomes, health system collapse, healthcare workforce, emergency obstetric care, low and middle income countries, health infrastructure disruption.

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Strictly as per the compliance and regulations of:

Stillbirths and Neonatal Deaths in Conflict Zones: A 10 Year Review of Health System Disruption and Collapse

Dr. Firi. L. Promise [α] & Dr. Peculiar Ihunwo [σ]

Abstract- Armed conflict significantly increases the risk of stillbirths and neonatal deaths, particularly in low and middle income countries (LMICs) where health systems are fragile or in active collapse. Over the past decade, countries such as Syria, Yemen, South Sudan, and Ukraine have experienced substantial deterioration in maternal and neonatal outcomes due to both direct and indirect effects of conflict. This paper employs a narrative synthesis of published and grey literature to assess the burden of perinatal mortality in conflict zones, with particular attention to trends in stillbirth and neonatal mortality, disruptions in service delivery, and the responses of global health actors such as UNICEF, the World Health Organization, and Médecins Sans Frontières. In several conflict-affected regions, stillbirth rates have reached forty per one thousand births, while neonatal mortality exceeds fifty per one thousand live births more than double the global average. Stillbirths, often underreported due to civil registration collapse and cultural stigma, remain largely invisible in humanitarian data systems. Through comparative analysis, the paper highlights critical intervention points and proposes conflict-adapted strategies such as mobile neonatal care units, community-based midwifery, and the use of humanitarian corridors to reduce preventable deaths.

Keywords: stillbirths, neonatal mortality, conflict-affected settings, maternal health, humanitarian response, perinatal outcomes, health system collapse, healthcare workforce, emergency obstetric care, low and middle income countries, health infrastructure disruption.

I. Introduction

a) Background

Perinatal mortality remains one of the most urgent and persistent public health challenges, especially in settings affected by armed conflict. Globally, approximately 1.9 million stillbirths and 2.4 million neonatal deaths are recorded each year, with over ninety percent of these occurring in low and middle income countries (Lawn et al., 2014; WHO, 2023). Conflict exacerbates these outcomes by dismantling health infrastructure, forcing healthcare workers to flee, interrupting the flow of medical supplies, and displacing vulnerable populations. The result is a sharp increase in preventable maternal and neonatal deaths.

Perinatal mortality encompasses both stillbirths and neonatal deaths. A stillbirth is defined as the birth of a baby with no signs of life at or after twenty-eight weeks of gestation, whereas neonatal death refers to the death of a live-born infant within the first twenty-eight days of life (WHO, 2023). While the clinical causes may vary, conflict amplifies the risk of both through shared pathways of health system disruption, nutritional deprivation, poor sanitation, and reduced access to skilled birth attendance.

Recent conflicts in Syria, Yemen, South Sudan, and Gaza provide stark examples of this dynamic. In Syria, the widespread bombing of hospitals and transport blockades severely limited access to obstetric care (Sparrow et al., 2016). Yemen's health system has been described as near-collapse, with only forty-five percent of health facilities functioning as of 2023, and maternal mortality increasing sharply in the wake of infrastructure breakdowns and medicine shortages (UNICEF, 2024). South Sudan, plagued by civil war and climate shocks, has recorded some of the world's highest rates of neonatal mortality, often in the absence of any skilled birth attendants (Makinde et al., 2025). Similarly, ongoing sieges in Gaza have led to frequent NICU shutdowns and an alarming rise in neonatal deaths from preventable conditions such as sepsis and hypothermia (The Guardian, 2024).

The breakdown of antenatal and postnatal services, lack of access to emergency obstetric care, and poor maternal nutrition contribute significantly to these outcomes. Displaced women are often forced to deliver in overcrowded, unsanitary shelters without adequate medical support. Additionally, structural failures such as electricity outages compromise the use of incubators and oxygen concentrators, rendering neonatal intensive care impossible (MSF, 2022).

Humanitarian interventions, though present in many of these settings, are often fragmented and underfunded. Organizations such as MSF, UNICEF, and WHO have deployed mobile neonatal units, initiated Kangaroo Mother Care (KMC) programs, and trained community-based midwives to close urgent gaps. However, the scalability and sustainability of these programs remain constrained by access, security conditions, and insufficient political will.

b) Objective

This paper reviews the trends in stillbirths and neonatal mortality over the past decade, from 2014 to

Author α: e-mail: pearlfiri6@gmail.com

2024, in conflictaffected low and middle income countries. Specifically, the objectives are fourfold:

- To quantify the extent of perinatal mortality in conflict settings using available data.
- To identify and analyze systemic drivers of neonatal and stillbirth outcomes during conflict.
- To evaluate the humanitarian interventions that have been implemented in response.
- To recommend evidence-based, context-sensitive strategies for improving neonatal survival in war-affected environments.

This analysis draws from peer-reviewed literature, humanitarian agency reports, and field evaluations to provide a comprehensive and policy-relevant synthesis of perinatal health outcomes in settings of armed violence.

II. Methods

a) Review Strategy

This review adopted a narrative synthesis methodology, incorporating key principles from systematic review frameworks to ensure transparency and rigour. The choice of narrative synthesis was based on the considerable heterogeneity of data types, the variation in outcome reporting across conflict settings, and the frequent reliance on grey literature and humanitarian reports, which are not easily meta-analysed. Methodological standards outlined by the Synthesis Without Meta-analysis (SWiM) guidelines informed the approach.

Database searches were conducted across PubMed, EMBASE, Scopus, and Web of Science for publications between January 2014 and January 2024. The search terms included combinations of Medical Subject Headings (MeSH) and free-text keywords, such as: “neonatal mortality,” “stillbirth,” “perinatal outcomes,” “armed conflict,” “war zones,” “maternal health,” “humanitarian response,” “health system collapse,” and “low- and middle-income countries.” Boolean operators (AND, OR) were used to optimize results. For example: (“neonatal mortality” OR “stillbirth”) AND (“conflict zones” OR “war”) AND (“maternal health” OR “obstetric care”).

Grey literature was included to capture humanitarian data often omitted in academic publishing. Sources included organizational reports and situation updates from the World Health Organization, UNICEF, Médecins Sans Frontières (MSF), Save the Children, UN OCHA, UNFPA, and The Guardian. These documents were assessed for credibility based on issuing body, publication date, internal consistency, and data traceability. News outlets were only included when corroborated by humanitarian sources or when providing verified field-level observations.

A total of 238 records were initially retrieved. After removing duplicates, 183 abstracts were screened. From this, 91 full texts were reviewed, with 54 publications ultimately included based on relevance, data integrity, and focus on stillbirths or neonatal mortality in conflict-affected low- and middle-income countries.

b) Inclusion and Exclusion Criteria

Studies and reports were eligible for inclusion if they:

- Reported on stillbirths or neonatal mortality in conflict-affected LMICs.
- Included quantitative data or empirical program evaluations.
- Were published between January 2014 and January 2024.
- Were written in English.

Exclusion Criteria Included:

- Opinion or commentary pieces without original data.
- Studies focused on high-income or non-conflict settings.
- Reports lacking information on perinatal health outcomes.

c) Country Selection Criteria

Eight countries were included in the analysis based on the severity and duration of armed conflict, the availability of neonatal health data, and regional representation. These countries are Syria, Yemen, South Sudan, Ethiopia (Tigray region), Sudan (South Darfur), Gaza, Iraq, and Ukraine (Donbas region). This selection enables cross-comparison across different geopolitical, cultural, and health system contexts.

d) Limitations and Review Rationale

Due to constraints in accessing real-time primary data from active war zones, the review relied heavily on grey literature and field reports. Many conflict settings lack centralized data collection systems, and figures may be underreported due to insecurity or political sensitivities. To address these limitations, data were triangulated from multiple credible sources whenever possible.

Although a full systematic review was not feasible, methodological transparency was prioritized throughout. A PRISMA-style flowchart summarizing the search and selection process is included in Figure 1.

Stage	Number of Records
Records identified from databases	238
Duplicates removed	55
Titles and abstracts screened	183
Full-text articles assessed	91
Publications included in review	54

Figure 1: Summary of Search and Selection Process (PRISMA-style Narrative)

III. Global Burden of Perinatal Mortality in Conflict Settings

Perinatal mortality refers to the combined measure of stillbirths and early neonatal deaths, typically occurring from the twenty-eighth week of gestation through the first seven days of life. In public health terms, however, perinatal mortality is increasingly interpreted more broadly to include all neonatal deaths occurring within the first twenty-eight days after birth, aligning with WHO monitoring indicators (WHO, 2023).

Stillbirths and neonatal deaths are two of the most critical indicators of maternal and child health system performance. A stillbirth, by WHO definition, is the birth of an infant with no signs of life at or after twenty-eight weeks of gestation. In contrast, neonatal mortality refers to the death of a live-born infant within the first twenty-eight days of life (UN IGME, 2022). Together, these outcomes signal the extent to which health systems are functioning, particularly regarding access to antenatal care, intrapartum monitoring, skilled birth attendance, and postnatal support.

In 2021, the global stillbirth rate stood at 13.9 per 1,000 total births, while the neonatal mortality rate was 17.5 per 1,000 live births. However, in conflict-affected low and middle income countries, these figures are dramatically higher, often surpassing 35 to 40 stillbirths and over 50 neonatal deaths per 1,000 births (UN IGME, 2023; WHO, 2023). These levels are far above the Sustainable Development Goal 3.2 targets, which aim to reduce neonatal mortality to fewer than twelve per 1,000 live births and eliminate preventable stillbirths by 2030 (United Nations, 2015).

In Yemen, where ongoing conflict has devastated infrastructure, the estimated stillbirth rate reached thirty-eight per 1,000 births, while neonatal mortality spiked between forty-five and sixty per 1,000 live births depending on the region (UNFPA, 2021; ReliefWeb, 2022). South Sudan presents similarly grave figures, with regional variations showing stillbirth rates as high as thirty-six per 1,000 and neonatal mortality averaging forty-three per 1,000 live births (Makinde et al., 2025; Save the Children, 2021).

The Donbas region of Ukraine has experienced a notable deterioration in neonatal outcomes since the onset of conflict in 2014. Prior to the war, neonatal mortality was estimated at nine per 1,000 live births. However, by 2021, this figure had increased to twenty-two per 1,000, largely due to the collapse of obstetric care networks and restricted humanitarian access (UN OCHA, 2021). In northeast Nigeria, areas affected by Boko Haram insurgency reported stillbirth rates of thirty-seven per 1,000 births, which is almost three times the national average (ACAPS, 2022).

These elevated mortality rates are not isolated anomalies, but rather recurring patterns in fragile settings where healthcare infrastructure, governance, and access are severely compromised.

Country	Stillbirth Rate (per 1,000)	Neonatal Mortality Rate (per 1,000)	Source(s)
Yemen	38	45–60	UNFPA, 2021; UNICEF, 2022
South Sudan	30–36	43	Makinde et al., 2025; Save the Children, 2021
Syria (Aleppo)	40	49	WHO EMRO, 2018; Sparrow et al., 2016
Ukraine (Donbas)	18–22	22	UN OCHA, 2021
Nigeria (Borno)	37	Not available	ACAPS, 2022
Gaza	Approx. 32	47	The Guardian, 2024; MSF, 2022

Figure 2

These figures underscore the magnitude of perinatal loss in conflict-affected settings and highlight the urgent need for a re-prioritization of maternal and newborn health in humanitarian response strategies.

IV. Drivers of Perinatal Mortality in Conflict Zones

The relationship between armed conflict and elevated rates of stillbirth and neonatal mortality can be understood through a combination of direct and indirect drivers. These mechanisms operate simultaneously and often synergistically, compounding existing vulnerabilities in fragile health systems. Understanding these pathways is essential for designing effective, context-specific interventions.

a) Direct Drivers: Violence and Systemic Destruction

The most immediate and visible drivers of perinatal mortality in conflict settings are those that result directly from acts of violence. These include deliberate attacks on health facilities, the physical endangerment of pregnant women, and blockade-related disruptions to access and transport.

Attacks on hospitals, maternity wards, ambulances, and other health infrastructure are well-documented violations of international humanitarian law. Between 2018 and 2022, more than 1,200 such attacks were verified globally, with the frequency increasing in 2023 (WHO, 2023). In Aleppo, Syria, the destruction of maternity hospitals during airstrikes forced pregnant women to give birth in overcrowded homes, often without skilled assistance or sterile equipment. In one instance reported by Médecins Sans Frontières, five neonates died in a twenty-four-hour period following the bombing of the only functional NICU in the region (MSF, 2022).

Blockades and siege conditions represent another form of violence with indirect but deadly consequences. In Yemen, the blockade of Hodeidah port severely restricted the importation of essential medical supplies including oxygen cylinders, neonatal antibiotics, and sterile birth kits. Without these resources, health workers reported sharp increases in intrapartum stillbirths and early neonatal deaths due to sepsis and birth asphyxia (UNICEF, 2021).

Conflict also increases the risk of obstetric trauma. Pregnant women exposed to physical violence or chronic fear are more likely to experience preterm labour, uterine rupture, or stillbirth. Studies from the Democratic Republic of Congo and Sierra Leone have shown significantly higher rates of miscarriage and stillbirth in women subjected to sexual violence during armed conflict (Amowitz et al., 2002).

b) Indirect Drivers: Displacement, Malnutrition, and System Collapse

Beyond immediate violence, conflict sets off a cascade of indirect effects that deeply influence perinatal outcomes. Among these are displacement, maternal malnutrition, the collapse of human resources, and infrastructural breakdowns in the broader health system.

Forced displacement disrupts antenatal care and increases the likelihood of home births in unsafe and unhygienic environments. In South Sudan, more than seventy percent of internally displaced women in camps reported no access to antenatal services, and a majority gave birth without skilled attendants. Deliveries in crowded shelters or tents often lack sterile tools, clean water, or any means of thermal regulation. This has led to high rates of neonatal sepsis, hypothermia, and birth asphyxia (Save the Children, 2021).

Maternal malnutrition, both acute and chronic, contributes significantly to poor birth outcomes. Conflict-affected areas frequently suffer food insecurity and famine-like conditions. In Yemen and South Sudan, over forty percent of pregnant women were identified as acutely malnourished in recent assessments (Makinde et al., 2025; UNICEF, 2022). Malnutrition leads to intrauterine growth restriction, low birthweight, and increased susceptibility to infection in newborns, thereby contributing to both stillbirth and neonatal mortality.

The loss of skilled personnel compounds these issues. Conflict often forces doctors, midwives, and nurses to flee, leaving health facilities either understaffed or completely inoperable. In Syria, it is estimated that seventy percent of the pre-war health workforce is no longer active, due to death, displacement, or migration (WHO EMRO, 2020). This personnel crisis means that even functioning facilities may be incapable of managing complications such as obstructed labour or neonatal resuscitation.

c) Health System Failure through the WHO Building Blocks

The collapse of health systems in conflict zones can be further understood using the World Health Organization's six building blocks framework: service delivery, health workforce, information systems, medical products and technologies, financing, and leadership or governance (WHO, 2007).

Service Delivery: Is typically the first to collapse. Maternity wards may be destroyed, operating hours limited due to insecurity, and essential services like emergency obstetric care rendered unavailable. This results in an increase in unattended home births, delayed referrals, and higher rates of intrapartum complications.

Health Workforce: Attrition follows swiftly. Conflict causes death, injury, flight, or psychological burnout among frontline health workers. For instance, in northeast Nigeria, only one obstetrician remained in Borno State to serve more than one million displaced people at the height of the Boko Haram insurgency (ACAPS, 2022).

Health Information Systems: Are often suspended or dismantled entirely during prolonged crises. Without functioning civil registration and vital statistics systems, stillbirths go uncounted and neonatal deaths

underreported. This obscures the true scale of the problem and undermines efforts to design effective interventions.

Medical Supply Chains: Break down under conditions of war. Delays in delivering vaccines, antibiotics, and neonatal resuscitation kits have been reported across Gaza, Yemen, and Ukraine. In Gaza, electricity blackouts also prevent the operation of oxygen concentrators and incubators, contributing to neonatal deaths from hypoxia and hypothermia (The Guardian, 2024).

Health Financing: Systems suffer major disruptions. National health budgets are diverted to military expenditure, and donor fatigue reduces external support. Out-of-pocket expenses for care increase, pushing families to delay or forego seeking services.

Lastly, *governance and leadership* structures often collapse or become fragmented. Ministries of Health may lose jurisdiction over parts of a country, or health policies become unimplementable due to loss of territorial control. In the Tigray region of Ethiopia, international health actors were blocked from accessing maternity clinics for months, resulting in catastrophic declines in service availability (UN OCHA, 2022).

V. Regional Case Studies in Conflict-Affected Perinatal Health

To ground the broader analysis in specific national contexts, this section presents focused case studies from four conflict-affected countries: Syria, Yemen, South Sudan, and Ukraine. These countries were selected due to their prolonged conflicts, significant perinatal mortality trends, and availability of humanitarian and academic data. Each case illustrates how conflict disrupts maternal and neonatal health through both direct and indirect pathways, as discussed in Section 4.

a) *Syria (2011–2024): Health System Collapse and Urban Siege Conditions*

The Syrian conflict offers one of the clearest examples of systemic collapse affecting maternal and neonatal outcomes. Prior to the war, Syria had among the highest rates of skilled birth attendance in the region, with approximately 96 percent of deliveries taking place in health facilities. By 2016, that figure had fallen below 60 percent in areas such as Aleppo, Homs, and Idlib, where aerial bombardment destroyed maternity hospitals and forced repeated evacuations of health personnel (Sparrow et al., 2016).

During the siege of eastern Aleppo, neonatal mortality rose sharply, with estimates reaching forty-nine deaths per 1,000 live birthsnearly three times the pre-war baseline. Field reports from Médecins Sans Frontières documented a complete collapse of neonatal intensive care services following the bombing of the city's largest NICU. Premature infants, many born to malnourished and anaemic mothers, died from sepsis, hypoxia, or cold exposure due to a lack of electricity and incubators (MSF, 2022).

Humanitarian responses were severely constrained by access restrictions. Nonetheless, international NGOs established mobile units equipped with portable oxygen tanks and solar-powered infant warmers in areas accessible by road convoys. These efforts improved outcomes modestly in peri-urban zones, but urban siege environments remained largely unreachable by 2020.

b) *Yemen (2015–2024): Blockades and Fragmented Governance*

Yemen's ongoing war has led to one of the world's worst humanitarian crises, with major impacts on maternal and neonatal health. As of 2023, only 45 percent of health facilities in the country were fully functional, and less than a quarter of births occurred with a skilled attendant present (UNFPA, 2023; UNICEF, 2022). Stillbirth rates have been recorded at thirty-eight per 1,000 births nationally, with even higher figures in the northern provinces. Neonatal mortality fluctuated between forty-five and sixty per 1,000 live births, depending on access to functioning services.

Fuel blockades and airstrikes on transport networks severely limited ambulance availability and referral systems. In Hajjah and Taiz governorates, pregnant women often walked more than five kilometres to reach care, only to find NICUs without functioning incubators or antibiotics. One field report recorded a survival rate of less than thirty-three percent among neonates admitted to neonatal wards in Hajjah in 2021 (ReliefWeb, 2022).

In response, UNFPA and Save the Children launched a mobile midwifery program that trained and deployed over 500 female birth attendants into remote villages and displacement camps. These workers carried solar-lit delivery kits, misoprostol for postpartum hemorrhage, and neonatal resuscitation tools. Additionally, solar-powered incubator prototypes were tested in two rural clinics, improving neonatal survival by nearly 40 percent in those sites over a nine-month pilot period (UNFPA, 2023).

c) *South Sudan (2013–2024): Conflict, Climate, and Isolation*

South Sudan presents a complex case of compounded crises, where conflict, floods, and famine intersect. Since its independence, the country has experienced near-continuous conflict and displacement. Neonatal mortality currently stands at forty-three per 1,000 live births, with stillbirth rates ranging from thirty to thirty-six per 1,000 depending on region (Makinde et al., 2025). Jonglei and Unity states, most affected by violence and displacement, report some of the country's worst perinatal indicators.

Access to skilled care is severely limited. In many regions, fewer than 20 percent of deliveries occur in health facilities, and antenatal care coverage is below 35 percent (Save the Children, 2021). Infrastructure is virtually non-existent in swampy and flood-prone areas. During the rainy season, communities become entirely cut off from health services.

To address this, community-based birthing huts have been established using locally available materials, staffed by women from the community who receive WHO-supported midwifery training. These huts provide clean delivery environments, thermoregulation tools, and emergency transport via canoe or motorcycle stretcher to secondary-level facilities. Although limited in scale, these efforts have demonstrated reductions in neonatal sepsis and birth complications in the regions where implemented (WHO ENAP, 2022).

d) Ukraine (2014–2024): Infrastructure Degradation in a Middle-Income Country

The Donbas region of Ukraine has experienced persistent conflict since 2014. As a middle-income country with a relatively strong pre-war health system, Ukraine presents a different set of challenges and adaptations. Between 2014 and 2021, neonatal mortality in the Donbas region increased from nine to twenty-two per 1,000 live births, largely due to the degradation of health infrastructure, staffing shortages, and disrupted supply lines (UN OCHA, 2021).

Approximately 30 percent of obstetric and neonatal facilities in the region were reported non-functional by 2022. Rural health posts lacked access to oxygen, heating, and incubator equipment during the winter months. COVID-19 further delayed humanitarian responses, leading to critical care shortages.

Médecins Sans Frontières deployed mobile neonatal stabilization units to eastern Ukraine beginning in 2020. These teams, equipped with portable resuscitation kits and thermal blankets, operated along the conflict line and provided on-site care to over 1,000 neonates by 2023. Preliminary evaluations indicate a 25 percent reduction in early neonatal deaths in their areas of operation (MSF, 2023).

e) Nigeria (Borno State)

Borno State in northeastern Nigeria has endured prolonged violence from the Boko Haram insurgency since 2009. Between 2013 and 2020, the region recorded persistently high stillbirth rates, peaking at 37 per one thousand births (ACAPS, 2022). Health services have been severely disrupted by attacks on clinics, abduction of health personnel, and widespread displacement of civilians.

Many pregnant women give birth in overcrowded internally displaced persons (IDP) camps, where basic sanitation, sterile delivery environments, and medical staff are lacking. Humanitarian access remains intermittent, and maternal health services have struggled to recover. Neonatal mortality estimates remain incomplete due to poor surveillance, but field reports suggest that newborn sepsis and birth asphyxia are common.

f) Darfur (Sudan)

Years of ethnic conflict and displacement in Darfur have resulted in some of the worst maternal and neonatal health indicators in the region. Over half of all births in conflict-affected areas occur outside formal facilities, often attended by untrained traditional birth attendants. Stillbirth estimates from camp settings vary, but surveys conducted in 2020 found rates as high as 32 per one thousand (UNICEF, 2022).

g) Rohingya Refugee Camps (Cox's Bazar, Bangladesh)

More than 900,000 Rohingya refugees have been displaced to Bangladesh since 2017, creating one of the largest stateless and displaced populations in the world. In overcrowded camps at Cox's Bazar, conditions for maternal and neonatal care are dire. A 2019 UNHCR report noted a neonatal mortality rate of 44 per one thousand live births (UNHCR, 2019). Stillbirths were frequent but underreported due to weak registration systems and cultural stigma.

Deliveries are often conducted in tents or makeshift shelters, with limited access to skilled attendants, electricity, or sterile equipment. While NGOs like MSF and Save the Children have established field maternity units, demand consistently outpaces capacity.

Neonatal care is virtually absent in many areas. Clinics are underequipped, referrals are slow, and neonatal resuscitation equipment is rare. Flooding and seasonal access problems further isolate rural communities. WHO and UNFPA have piloted some mobile units in central Darfur, but coverage remains highly limited.

h) Gaza Strip (Occupied Palestinian Territory)

The Gaza Strip, under blockade since 2007 and frequently affected by conflict, presents one of the most densely populated and chronically unstable health environments. Neonatal units in public hospitals often run without consistent power, oxygen, or clean water. A 2023 field report by UNICEF and The Guardian documented a neonatal mortality rate approaching 47 per one thousand live births, with stillbirths occurring in delivery rooms lacking functional incubators or resuscitation equipment (The Guardian, 2024).

The blockade has severely restricted access to medicines, spare parts for medical devices, and mobility for referrals. Despite the presence of skilled health personnel, resource constraints and repeated infrastructure damage continue to undermine neonatal survival.

VI. Humanitarian Actors in Neonatal and Stillbirth Response

Humanitarian agencies play a central role in mitigating the consequences of conflict on maternal and newborn health. Organizations such as the United Nations Children's Fund (UNICEF), Médecins Sans Frontières (MSF), the World Health Organization (WHO), the United Nations Population Fund (UNFPA), and the International Committee of the Red Cross (ICRC) have developed a range of strategies to reduce perinatal mortality in settings where national health systems have collapsed.

UNICEF has been a lead agency in scaling up community and facility-based neonatal care in emergencies. Its maternal and newborn health response includes distribution of clean birth kits, promotion of kangaroo mother care (KMC), and deployment of emergency obstetric teams to underserved regions. Between 2020 and 2023, UNICEF distributed over 150,000 clean delivery kits in Yemen, Syria, and South Sudan alone (UNICEF, 2023). These kits provided critical supplies such as sterile blades, gloves, thermal blankets, and antiseptic to women delivering in informal settlements and conflict zones.

The promotion of KMC, a lowcost intervention involving skin-to-skin contact and exclusive breastfeeding, has been one of the more scalable efforts in resource-constrained areas. UNICEF and WHO have supported KMC implementation in displacement camps and temporary clinics across Gaza, Tigray, and northeast Nigeria. Evaluations suggest that KMC has led to a 25 to 50 percent improvement in neonatal survival among low birthweight infants when implemented effectively in crisis settings (WHO, 2022).

MSF has taken a leading role in direct service delivery, particularly in hard-to-reach or besieged zones where access for larger agencies may be limited. MSF operates field hospitals and neonatal units in over thirty conflict zones, including eastern Ukraine, Syria, and South Sudan. Their model emphasizes training of local birth attendants in neonatal resuscitation, infection prevention, and clean delivery techniques. A 2022 evaluation of MSF-supported clinics in Unity State, South Sudan reported a 22 percent reduction in early neonatal mortality after six months of targeted intervention (MSF, 2023).

Despite these contributions, major limitations remain. Humanitarian coordination is often fragmented, with duplication of services in accessible areas and total absence in others. In Yemen, for instance, overlapping mandates between WHO, UNFPA, and national authorities led to confusion over the provision of reproductive health supplies in 2021, leaving some regions overstocked and others dangerously under-resourced (ReliefWeb, 2022). Furthermore, political barriers such as blockades, security restrictions, or denial of humanitarian access hinder implementation in the most affected zones.

Data collection is another critical challenge. Stillbirths, in particular, remain underreported across humanitarian operations. Most field health information systems prioritize maternal deaths or under-five mortality, with stillbirths often classified inconsistently or omitted entirely from monitoring frameworks. This invisibility prevents adequate resource allocation and perpetuates the notion that stillbirths are unpreventable or secondary concerns (Flenady et al., 2016).

Perhaps most critically, structural challenges persist because humanitarian health interventions remain reactive rather than integrated. Emergency neonatal care is often mobilized late, following media attention or catastrophic events, rather than embedded within ongoing preparedness and response plans. Short-term funding cycles, reliance on temporary staffing, and limited support for local health governance mean that interventions, even when effective, are difficult to sustain or scale.

In summary, humanitarian actors have made significant contributions to mitigating perinatal mortality in conflict zones. Their efforts have saved lives, expanded access to critical care, and innovated in low-resource environments. However, without systemic coordination, sustained investment, and formal inclusion of stillbirth reduction in global response frameworks, these efforts risk remaining fragmented and insufficient.

VII. Discussion

This review has illustrated how armed conflict acts as a powerful disruptor of maternal and neonatal health in low and middle income countries. The evidence drawn from Syria, Yemen, South Sudan, and Ukraine consistently shows that perinatal mortality increases sharply when health systems are destabilized. These countries, though diverse in geography and political context, reveal remarkably similar patterns: healthcare facilities are destroyed or rendered non-functional, trained personnel are displaced or killed, and pregnant women are forced to give birth in unsanitary environments without medical support.

Direct consequences of conflict include the destruction of neonatal intensive care units, targeted attacks on maternity wards, and the obstruction of humanitarian supplies. In Aleppo, Syria, aerial bombardments led to the closure of functioning NICUs and forced expectant mothers to deliver in private homes or abandoned buildings. Médecins Sans Frontières reported that premature infants often died from hypothermia, birth asphyxia, or untreated infections due to the absence of incubators, power, and antibiotics (Sparrow et al., 2016; MSF, 2022). In Yemen, the blockade of Hodeidah severely restricted access to fuel, sterile birth kits, and oxygen cylinders, further increasing

the rate of intrapartum stillbirths and neonatal complications (UNFPA, 2021; ReliefWeb, 2022).

Indirect mechanisms are no less lethal. Displacement consistently undermines continuity of care. In South Sudan, the collapse of road infrastructure due to conflict and flooding has left many pregnant women without antenatal care or access to trained birth attendants (Makinde et al., 2025). These conditions contribute to higher rates of sepsis, obstructed labor, and perinatal asphyxia. Similarly, maternal malnutrition documented in over 40 percent of women in both Yemen and South Sudan is strongly associated with low birthweight and increased vulnerability to infection among newborns (UNICEF, 2022; Save the Children, 2021).

The role of humanitarian organizations in addressing these crises has been substantial but uneven. Mobile midwifery services, kangaroo mother care units, and emergency neonatal kits have helped to mitigate mortality in some regions. For example, UNFPA's deployment of solar-powered incubators in rural Taiz led to improved thermal care for premature infants, while MSF's field hospitals in Unity State reported a measurable reduction in early neonatal deaths following the introduction of community birth attendant training (UNFPA, 2023; MSF, 2023). However, these interventions are often limited in scale, delayed in implementation, and hindered by insecurity and political restrictions.

Stillbirths remain underreported across nearly all settings, in part due to the collapse of civil registration systems during conflict. Even where neonatal mortality data exist, stillbirths are frequently omitted or aggregated in ways that obscure their burden. The cultural stigma surrounding stillbirth, combined with the lack of standardized definitions and data tools, further compounds this problem (Flenady et al., 2016). As a result, humanitarian responses tend to overlook stillbirth prevention, focusing instead on maternal survival or postnatal care.

The health system perspective helps to clarify why perinatal mortality rises so dramatically during war. Using the World Health Organization's framework, it is evident that all six building blocks of health systems are severely compromised. Service delivery is interrupted by facility closures and staffing shortages. Human resources are depleted as skilled personnel flee violence. Health information systems become unreliable or are dismantled entirely. Supply chains for essential medicines and equipment are routinely blocked. Financing shifts toward military priorities, leaving reproductive health underfunded. Leadership and governance become fragmented or incapacitated, especially in regions where government control is lost or contested.

While many of the contributing factors to stillbirths and neonatal deaths are structural and long-standing, the evidence also points to areas of resilience and innovation. Local midwives, community health workers, and mobile response units have all played crucial roles in sustaining care where formal systems have collapsed. Where partnerships between humanitarian agencies and national health authorities are strong, such as in select regions of Ukraine and South Sudan, interventions have demonstrated greater consistency and coverage.

Nonetheless, the broader picture remains sobering. Perinatal mortality in conflict zones is not an unavoidable consequence of war, but rather the outcome of health system failure, global inaction, and inadequate policy attention. Without deliberate, well-funded, and context-specific interventions, the death of thousands of newborns will continue to go uncounted and unchallenged.

VIII. Recommendations

Reducing stillbirths and neonatal deaths in conflict settings requires more than isolated humanitarian interventions. It demands sustained policy commitment, stronger coordination among global health actors, and conflict-sensitive strategies that address both immediate and systemic failures. Based on the evidence presented in this review, the following recommendations are proposed to strengthen perinatal survival in crisis-affected environments.

a) Prioritize Perinatal Health in Humanitarian Strategies

Stillbirths and neonatal deaths must be elevated as core indicators within emergency health responses. Currently, these outcomes remain underrepresented in humanitarian reporting frameworks, despite their prevalence. Agencies such as the World Health Organization, UNICEF, and the Inter-Agency Standing Committee should incorporate perinatal mortality data including stillbirths into cluster-level monitoring systems and inter-agency response plans. Making perinatal survival an explicit objective will ensure that resources are allocated accordingly, and that stillbirth prevention is not sidelined.

b) Strengthen Protected Access through Humanitarian Birth Corridors

In settings where physical access to hospitals is obstructed by violence or geography, the establishment of humanitarian birth corridors is essential. These protected pathways must be negotiated with conflict parties and coordinated with local actors to guarantee safe passage for pregnant women, newborns, and emergency transport. Experience from eastern Ukraine and Gaza shows that such arrangements, though complex, are feasible and can significantly reduce delays in reaching obstetric or neonatal care.

c) *Scale up Community-based Neonatal Care*

When health systems collapse, trained community members often become the primary providers of maternal and newborn care. Expanding training for local midwives, community health workers, and birth attendants can increase coverage of essential interventions such as thermal protection, infection prevention, and neonatal resuscitation. The success of community birthing huts in South Sudan and mobile midwifery in Yemen demonstrates that localized models are not only feasible, but also culturally appropriate and cost-effective.

d) *Support Innovation in Mobile and Low-Tech Neonatal Services*

Investments in lowcost, contextadapted neonatal technologies can help bridge the gap left by dysfunctional hospitals. Tools such as solar-powered incubators, portable resuscitation packs, and kangaroo mother care units have shown success in field conditions. Scaling such innovations across humanitarian settings would require flexible funding mechanisms and better integration of these tools into national emergency preparedness plans.

e) *Integrate Mental Health Support into Maternal and Newborn Services*

Psychological trauma is a common consequence of both perinatal loss and conflict exposure, yet mental health is often excluded from maternal health programming. Services such as grief counselling for bereaved mothers and psychological support for frontline staff should be incorporated into the design of emergency obstetric and neonatal care. Pilot programs by Médecins Sans Frontières and WHO have shown that peer counselling and psychosocial first aid can be delivered even in resourceconstrained settings with appropriate training and community engagement.

f) *Improve Coordination and Sustain Long-Term Investment*

Effective response requires coordinated action across humanitarian, governmental, and technical partners. Overlapping mandates and inconsistent funding streams continue to fragment efforts. Establishing dedicated neonatal health coordination platforms within health clusters could improve planning, reduce duplication, and standardize care delivery. Furthermore, donors must transition from short-term funding cycles toward multi-year commitments that support infrastructure recovery, workforce rebuilding, and health information systems rehabilitation.

Together, these recommendations offer a pathway toward reducing preventable perinatal deaths in conflict zones. Each strategy is grounded in field-tested interventions or supported by data presented in this review. While conflict will likely remain a feature of the global landscape, the vulnerability of newborns does not have to be inevitable.

IX. Conclusion

Stillbirths and neonatal deaths in conflict zones represent one of the most overlooked public health emergencies of our time. Far from being random or unavoidable, these deaths are predictable outcomes of systemic neglect, structural collapse, and international inaction. The analysis presented in this paper shows that across Syria, Yemen, South Sudan, and Ukraine, the destruction of health infrastructure, loss of skilled personnel, collapse of supply chains, and displacement of vulnerable populations have created environments where safe childbirth is no longer guaranteed.

Yet these outcomes are not inevitable. The vast majority of stillbirths and neonatal deaths in these settings are preventable with timely, basic interventions clean delivery environments, skilled care during birth, access to oxygen, neonatal resuscitation, and postnatal warmth. Humanitarian efforts have shown that even under siege or in displacement, simple tools like kangaroo mother care, solar-powered incubators, and mobile birth kits can save lives when deployed effectively.

Despite international commitments under Sustainable Development Goal 3.2 to reduce neonatal mortality to fewer than twelve per one thousand live births and to eliminate preventable stillbirths by the year 2030, conflict-affected countries remain furthest from these targets. The global health community cannot afford to treat these settings as exceptions. Instead, they must become the focal point for innovation, funding, and accountability in perinatal health.

Ultimately, the right to survive the first day of life should not be conditional upon geography, peace, or privilege. As global instability continues to displace millions and threaten already fragile systems, newborns must be placed at the center of emergency response and recovery strategies. With sustained investment, coordinated action, and a commitment to perinatal inclusion in humanitarian frameworks, it is possible to protect the youngest and most vulnerable even in the most difficult of circumstances.

Abbreviations and Full Terms

1. LMICs – Low and Middle Income Countries
2. NMR – Neonatal Mortality Rate
3. WHO – World Health Organization
4. UNICEF – United Nations Children's Fund
5. MSF – Médecins Sans Frontières
6. NICU – Neonatal Intensive Care Unit
7. ICRC – International Committee of the Red Cross
8. UN OCHA – United Nations Office for the Coordination of Humanitarian Affairs
9. KMC – Kangaroo Mother Care

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Dualism of the Aging Process (Analytical Review)

By Vladimir N. Shabalin

Abstract- The aging process is one of the most complex problems in biology. Hundreds of research institutes around the world are studying aging at various levels of the structural organization of living matter. The results of many thousands of studies on this phenomenon have been published. More than 300 theories have been proposed that attempt to explain the causes of aging. It is important to note that almost all theories associate aging with the accumulation of negative changes in molecules and cells in the body. It seems that a person (or an individual of another biological species) lives in order to make negative changes in the structure of living matter. However, this contradicts the fact that damage and destructive changes cannot ensure progress in the evolutionary development of life.

Keywords: aging, evolution, biosphere, self-organization of living matter, collection, transformation, archiving and transmission of biological information.

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Abstract- The aging process is one of the most complex problems in biology. Hundreds of research institutes around the world are studying aging at various levels of the structural organization of living matter. The results of many thousands of studies on this phenomenon have been published. More than 300 theories have been proposed that attempt to explain the causes of aging. It is important to note that almost all theories associate aging with the accumulation of negative changes in molecules and cells in the body. It seems that a person (or an individual of another biological species) lives in order to make negative changes in the structure of living matter. However, this contradicts the fact that damage and destructive changes cannot ensure progress in the evolutionary development of life.

The article attempts to find the cause of this contradiction. The author puts forward a position on the dual function of the aging process in the development of living matter: on the one hand, aging causes degradation of the organism as a system, on the other, it ensures the structural improvement of its tissues at the molecular level. That is, aging, as the main mechanism of evolution, is aimed not at preserving the organism as a system, but at preserving its individual elements (information blocks) that are of interest for building new structures of living matter as a whole. An evolutionary ladder is formed from these information blocks, along which living matter rises to a higher level of its development. Aging is not decay or damage, but a mechanism for transferring one structure of living tissue to another - more perfect, with its preservation in the form of a potential phase for use by new cellular generations of the same organism or other organisms.

Keywords: aging, evolution, biosphere, self-organization of living matter, collection, transformation, archiving and transmission of biological information.

I. State of The Problem

The problem of aging has attracted biologists, physicians, philosophers, demographers, and recently representatives of the exact sciences - physicists, chemists, mathematicians, as well as economists, cultural scientists and other specialists for centuries. At the same time, there is still no generally accepted theory of aging in gerontology. Despite the obvious changes in the body during aging, the concept of "aging" remains vague. The reason for this situation is that life is a complex system consisting of many interacting elements with feedback loops, hierarchical structure, nonlinear dynamics and emergent properties [1]. All these dynamic elements of life are united by the principle of self-organization. So far, this great immanent principle remains a profound mystery [2]. According to modern scientific concepts, self-organization is the basis of the evolutionary development of living matter- all living beings acquire forms and functions as a result of self-organization [3]. Biological self-organization is directed and reinforced by natural selection, during which the most stable, flexible modular systems capable of further adaptation are preserved [4].

Prigogine demonstrated the possibility of the emergence of new properties and order in self-organizing systems - dissipative structures that are stabilized by energy exchange with the environment [5, 6]. Self-organization creates emergence - a phenomenon when new properties or new behavior arise in a system that its individual components do not have [7, 8]. The role of aging in the process of evolutionary self-organization is that it ensures the preservation of emergent properties that arise during the life of an organism. The relationship between a person and the microworld, animal and plant worlds is a fragment of a single coordinated information-analytical biospheric process. A person feeds on living matter - builds his tissues from structures created by various biological species. A person lives in an organic fog - a molecular, cellular, viral and other environment formed and thrown into the biosphere by various organisms. All of this enters the human body through the food, water and air cycles and is processed: structural information is extracted, which is assimilated in its tissues, ensuring its continuous development [9]. The aging process occupies a leading place in this development, covering numerous biomechanisms that ensure the diversity of its manifestations.

II. Scientific Approaches to Studying the Problem of Aging

Historically, there have always been two directions in science – reductionism ("understand more and more about less") and holism ("see more, neglecting less"). Today, there is a hypertrophied predominance of the first direction, which includes studying the problem of aging. However, it should be taken into account that we are simply not able to understand the system at the level of analyzing only its components [10]. Nevertheless, all existing hypotheses of aging are based on monofactorial analysis. Thus, I. Mechnikov saw the cause of aging in endogenous intoxication, L. Szilard - in radiation damage to chromosomes, A. Bogomolets - in connective tissue disorders, F. Sineks – in DNA errors, D. Harman - in tissue damage by free radicals, L. Orgel - in the

Author: Scientific Research Institute of General Pathology and Pathophysiology, Moscow, Russia. e-mail: shabalin.v2011@yandex.ru

synthesis of abnormal proteins. Like these popular theories, all the others also associate aging with the accumulation of negative changes in molecules and cells in the body. It seems that a person (or an individual of another species) lives in order to make negative changes in the structure of living matter. However, this contradicts the fact that damage and destructive changes cannot ensure progress in the evolutionary development of life. These and other numerous theories and hypotheses try to define a universal factor of aging. The following are proposed as such factors: mitochondrial dysfunction, oxidative stress, senile inflammation, impaired intercellular communication, genomic instability, telomere depletion, impaired proteostasis, epigenetic changes, depletion of stem cells and other causes [11]. Of course, it is very tempting to look for the cause of aging in some one factor, then it would be easier to find a means that radically changes the duration and quality of life of the organism. But, alas, the aging process includes all the numerous components (physical, chemical, biological, social) that ensure the dynamics of the organism's development.

According to some authors [11], the evolutionary hypothesis considers aging as one of the mechanisms that remove individuals who have lost the ability to reproduce from the population. However, firstly, all individuals will leave the population due to death, and secondly, individuals who have lost the ability to reproduce continue to remain in the population for a long time. Apparently, there is a certain evolutionary sense in this.

It should be noted that the listed and other theories and hypotheses try to determine a universal factor of aging. The following factors have been proposed: mitochondrial dysfunction, oxidative stress, senile inflammation, impaired intercellular communication, genome instability, telomere depletion, impaired proteostasis, epigenetic changes, stem cell depletion and other causes [12]. Of course, it is very tempting to look for the cause of aging in some one factor, then it would be easier to find a means that radically changes the duration and quality of life of the organism. But, alas, the aging process includes all the numerous components (physical, chemical, biological, social) that ensure the dynamics of the organism's development.

Most researchers divide the aging process into two main variants: aging is hereditarily programmed and aging is caused by external factors [13, 14, 15]. However, such a division contains an error, since it is impossible to consider these two main causes of aging in isolation from each other. During the life of an organism, they constantly act together and only their combination determines the nature of aging and life expectancy. The fundamental possibility of mutations in the cell's DNA is embedded in its program, but the specific type of mutation is determined by a mutagen - an external biological, chemical or physical factor.

Attempts are being made to find genes that ensure the lifespan of an organism [16]. But is there any gene that does not affect the lifespan of an organism? If such assumptions arise, then this is most likely the result of a far from complete study of the functions of the entire genetic apparatus. The influence of genetic factors on the lifespan of an organism can only be considered as a systemic function of the genome as a whole.

Playing along with people's unrealistic but passionate dreams of eternal youth, research is currently ongoing on rejuvenating the genome and slowing down the aging process [17]. The history of the search for the source of eternal youth begins in ancient times, as evidenced by the legacy we inherited from the fathers of ancient medicine, medieval alchemists, and experimenters of the New Age [18]. Alas, the thousand-year search for rejuvenation has not yet yielded even encouraging results.

The problem of aging appears completely different when moving from reduction analysis to systemic analysis. A systemic approach to the problem of aging can be implemented from the standpoint of interactomics, which studies the interactions between proteins and other molecules within a cell, between organisms, between biological systems and their environment. This allows us to consider the biosystem as a whole [19, 20, 21]. Interactomics shows that only the entire complex of inherited and acquired information concentrated in the organism resolves the issue of the possibility of developing all complex, highly dynamic interweaving of age-related changes throughout the entire period of the organism's existence. It is interactomics, by forming the logistics of the development of living nature, that helps to avoid mutual misunderstanding in the scientific community.

III. Aging and Pathology

Along with the problem of aging in the evolutionary movement of life, the problem of pathology remains far from clear. The division of the concepts of "health" and "disease" is considered conditional, and the medical norm, which includes a wide range of healthy and pathological conditions, is identical to the biological norm [22]. Pathological forms of aging, like physiological aging, play a dual role: on the one hand, they burden the vital activity of the organism, and on the other, they contribute to the emergence of specific structures that provide resistance to negative environmental factors. Even Lactantius noted in the 4th century: "All disasters - both of all mankind and of individuals, are not useless and lead mankind, albeit in a roundabout way, to the same one goal that is set for people - improvement" [23].

In the process of natural selection, the body's response to the ongoing action of pathogenic factors gradually acquires an expedient, adaptive character. Non-specific adaptation factors are replaced by specific ones based on adequate complication of structure and function. According to the morbid concept of organic progress, to complicate the internal structure of the organism, it is not enough to change only the external conditions of existence (this is a way of idioadaptation), a stable change in the internal conditions of existence (disease) is also necessary [24].

No organism ever exists in a state of purely physiological development, its vital activity is a pathophysiological transformation of its own tissues [25]. That is, evolution always invests in its “working tools” (organisms) in various proportions and variants both components of the development of living matter – physiological and pathological. This connection has existed inseparably throughout the history of the development of life and is preserved as one of the basic principles of the transformation of the structure of living matter. Pathology is a special way of collecting biological information, different from the physiological one. During the period of illness of the organism, molecules, crossing the physiologically permissible boundaries of conformation, form non-standard structures that provide it with special forms of adaptation (maladaptation). In the evolutionary process, maladaptation plays no less an important role than physiological adaptation. Disadaptation “breaks” the previous systems of the organism, formed in the process of phylogenetic and ontogenetic development, reduces the vital activity of organisms and therefore, as a momentary phenomenon, has a negative meaning, but in evolutionary terms it has a tremendous positive meaning [26]. That is, the disease is a “non-standard” vector of evolutionary development.

According to Weismann's postulate, all biological individuals are united by a common phenotype and a single program for its construction (genotype), transmitted by inheritance [27]. Individuals and species of living nature are not independent objects of evolution, but work in the unity of genetically determined methods of qualitative transformation and growth of information archives of living matter and cannot exist outside this unity. Only the closest integration of biological species and individuals, different in their genetically determined specificity, forms mutually complementary methods of analyzing the information content of the internal and external environment of organisms. Integration ensures the development of the systemic structure of the biosphere, the accumulation of potential and kinetic energy in it, which is the essence of the total "aging" of living matter.

IV. Proteins as the Main Creators and Keepers of Somatic Information

Proteins account for about 50% of the mass of a living cell. Each nuclear cell produces protein molecules, providing proteostasis - dynamic regulation of a balanced proteome. One part of the created protein molecules is used for intracellular reparative processes, the other part (secretome) is released into general circulation. More than 10,000–13,000 types of different proteins are expressed in human cells [28].

The protein molecule does not have a static form; as a result of metabolism and the action of environmental factors on the organism, it is in the process of continuous conformational transformations. Conformation (folding) of protein molecules is the initiating factor of the evolutionary transformation of living matter. In order to understand the general dynamics of biological processes at the level of the microworld of the organism, it should be taken into account that the total number of protein molecules in the human organism (presumably about 11^{15}) multiplied by the potential folding capabilities provides the broadest potential for finding the most effective tissue structures of living organisms in the process of evolutionary development [29, 30, 31, 32].

A protein molecule is not only a building block of life, but a complex information mechanism that constantly collects information, adapts, changes and transmits the accumulated "knowledge" to the structures of its own organism and the biosphere, ensuring the continuity of life in its diversity [33, 34]. Stable or transient protein-protein interactions form the basis of regulation and control within the cell through the transmission of internal and external signals [35]. Proteins, their associations and aggregations are essential for many processes that play a key role in various biological phenomena, from intercellular signaling to the development of diseases [36, 37, 38]. Figuratively speaking, protein molecules are the strings on which the main melody of life is played.

The quinary structure of the protein deserves special attention when analyzing the mechanisms of aging. It is the fifth level of protein complexity in addition to the primary, secondary, tertiary and quaternary structures [39, 40, 41]. In order to perform their functions, proteins often need to find a specific analogue with which (for archiving information) they will bind for a relatively long time. In the very crowded cytosol, in which proteins engage in a vast and complex network of attractive and repulsive interactions, such a search becomes a difficult task because it involves sampling a huge space of possible partners, of which very few will be productive. The solution to this problem requires that proteins spend as little time as possible on each encounter, so that they can explore a large number of surfaces, while simultaneously making this interaction

as intimate as possible, so that if they do encounter the right partner, they make firm contact. In this sense, the quinary structure is the result of a number of adaptations present on the surface of proteins that allow proteins to navigate the complex cellular environment [42]. It can be assumed that during the aging process, the molecule, as a result of collecting information, enters the fifth stage of folding - it is folded into an archival cocoon (a concentrate of basic information) - the result of the molecule's vital activity. In the final phase, the molecule can be metabolized by its own organism, or thrown into the biosphere in the form of an "information quantum" that is used by other organisms. Such transformations of protein molecules that are part of the cell structure, as they accumulate, determine the aging of the cell.

New structural information is transferred by the secretom of protein to the genome of somatic cells, where the issue of its preservation at the genetic level and transmission to daughter cells is decided [43, 44, 45].

Thus, it is difficult to imagine the enormous amount of work that a protein molecule performs throughout its life. But this work is the basis of evolution. The property of a protein molecule to change its structural form exceptionally quickly, breaking some chemical bonds and creating others in response to changes in the chemical composition of the environment, allows it to “calculate” thousands of thousands of different structural variants and select the most effective ones for building the most perfect forms of living matter. The selected variants are supplied with strong chemical bonds and are stored in the “archive blocks” of the structure of organic molecules. When the “archives” are filled, the molecule loses its functional (analytical) capabilities, the process of its conformation stops and (as one of the options) its disintegration begins. However, the blocks (oligopeptides) and amino acids of disintegrating protein molecules retain specific structures created by the organism, which transmit the corresponding information to new molecules formed inside the organism or, when they enter the biosphere, to the molecules of other organisms. Thus, the aging process is not an age-related degradation of the organism, but a “cocooning” of information collected by it during life.

V. Genome Transformations during the Aging Process

The existing classification of biological variability types contains many contradictions, which often serves as a source of mutual misunderstanding between biologists. There is still no generally accepted definition of mutation that would separate it from other types of variability [46, 47, 48, 49]. In particular, epigenetic changes also do not have a clear definition; they are often classified as processes close to mutations, and the term "epimutations" is used [50]. To avoid these contradictions, it may be appropriate to classify all changes in the information encrypted in the DNA structure as mutations [51].

The stage-by-stage development of an organism (zygote, embryo, fetus, newborn, stages of youth, maturity, old age and old age) occurs in "steps" of genome mutation and protein folding [52, 53]. In addition to the genetic information passed down from generation to generation, each organism is born with a small number of new genetic changes (de novo mutations) that occurred either during gamete formation or at the postzygotic stage. As the organism develops, new mutations continue to arise throughout postnatal and adult life in both somatic and germ cells [54]. With each age stage of the organism, its genome and somatic cell proteins collect information from external and internal signals, transform it, and create structural archives in the tissues of the organism. These archives occupy corresponding volumes in the structure of cells, thereby reducing their functional activity, which is generally expressed in their aging.

A systematic study conducted on different mammal species showed that the frequency of somatic mutations is the main factor of aging [55]. Again, objective results of the study of age-related DNA changes are interpreted only as damage [56, 57, 58, 59, 60]. At the same time, when analyzing the role of mutations in the aging process, it should be taken into account that in many cases, the so-called DNA damage itself does not affect the functionality and performance of the cell [61]. Moreover, as some researchers note, disturbances in the genetic apparatus of the cell during aging can lead to the activation of genes that have been “silent” throughout life [62]. Of course, such changes cannot be attributed to damage. It is also interesting that mutations that were previously considered unnecessary can become useful and increase the survival of a given organism and its descendants [63].

The direct causes of DNA damage include a whole range of biochemical transformations: deamination of amino acids [64], glycation of proteins [65], shortening of telomeres [66] and many other reasons. Starting with L. Orgel [67], subsequently almost all modern researchers believe that with aging, the accumulation of DNA damage increases [68, 69], that after each cell division, degradation of genetic information contained in the chromosome occurs [70, 71]. According to the error theory, age-related mutations in cellular DNA entail the synthesis of altered RNA, and this in turn leads to the synthesis of altered proteins. Altered proteins induce the synthesis of "incorrect" ribonucleic acids - a vicious circle arises. However, all these and other numerous mechanisms involved in age-related transformations of tissue structures are more likely to be regarded as adaptive mechanisms than as negative factors. Why should all mutations be

considered as damages that cause cell dysfunction? Malicious DNA - in the physiological development of the aging process? No, these are not malicious DNA, but transformed genetic structures that carry new information collected during their life cycle.

VI. Epigenetic Modifications in Cell Aging

Recent studies have shown that epigenetic modifications play a key role in cellular aging [72]. DNA plasticity is partly due to epigenetic changes that affect cell function and can be transmitted to future generations [73]. DNA in the body is constantly disturbed by DNA-manipulating proteins [74]. Protein-DNA interactions provide feedback between genotypes and phenotypes [75, 76, 77]. These interactions indicate the exchange of information between genetic and somatic structures. The mechanisms of epigenetic variability represent a very diverse group of phenomena [78]. Age-related epigenetic changes include DNA methylation, histone modification, chromatin remodeling, regulation of non-coding RNAs and other modulating actions [79, 80]. Among the listed epigenetic factors of evolutionary transformation of the genome, DNA methylation is the most studied act. DNA methylation is considered to be a mechanism for implementing programmed aging [81]. DNA methylation activity can change and regulate gene expression depending on age [82]. Global DNA methylation levels increase during the first few years of life and then decrease starting in late adulthood [83]. Such dynamics of methylation activity indicate a physiological role of this process. It is important to note that epigenetic modifications are reversible: DNA methyltransferases, demethylases and associated proteins dynamically demethylate DNA [84, 85]. That is, it can be assumed that the cell is undergoing a process of rechecking and in-depth processing of information collected by the cell.

The role of gene regulatory networks in the aging process is performed by epigenetic regulators responsible for the reorganization and strengthening of certain chromatin structures [86]. During aging, chromatin becomes less active and compacted, and the connections between DNA and chromatin proteins also become stronger [87, 88]. These changes may indicate the archiving of information and the formation of protection of information structures from enzymatic destruction.

VII. Participation of Extracellular Nucleic Acids in the Formation of Biological Memory

Information probing in the body, along with proteins, is also carried out by extracellular (circulating) nucleic acids (cir-nNA). They are present in blood plasma, cerebrospinal fluid, saliva and other body fluids [89]. Extracellular DNA can penetrate cells with subsequent incorporation into their genome [90]. The presence of cir-nNA in the circulating fluids of the body indicates the existence of a special pathway for the transfer of genetic information between cells of various tissues of the body and participation in their transformation [91].

Thus, the body is constantly actively working to correct DNA changes, select useful information and eliminate living matter that is unpromising for further development. Mutations form new structures of body tissues that carry new functions and determine the limits of evolutionary trajectories [92]. As a result of the continuous collection of information by organic molecules coming from the external or internal environment and its delivery to the genome of somatic cells, mutations occur - a change in the genome that is passed on to the descendants of a given cell. The most significant mutations of somatic cells in the process of evolution can be transmitted to the genome of germ cells and change the gene pool of a biological species [93]. Figuratively speaking, life is a game of parts of a system with its environment. In such a game, a living system remembers successful decisions made in previous rounds and uses them to search for more perfect decisions in subsequent rounds.

VIII. DNA Repair System

Of particular importance is the notion that the rate of aging is determined by the relationship between damaging factors on the one hand and tissue repair factors on the other. Cells have several mechanisms for repairing and overcoming DNA damage. The main and most universal mechanism used by mammalian cells to remove altered bases or nucleotides in DNA is known as base excision repair (BER). BER involves several enzymes, including DNA-glycosylases, AP-endonucleases, DNA-polymerases, DNA-ligases, and accessory proteins, which act sequentially on the same damaged DNA site. Instead of associating into a single stable multisubunit complex, these enzymes pass repair intermediates between themselves in a highly coordinated manner [94, 95, 96]. If the DNA damage is repaired, the cell cycle continues. Otherwise, molecular mechanisms are activated: either senescence or apoptosis [97]. Senescent (old) cells are metabolically active, but do not divide. They do not respond to growth factors and are resistant to apoptosis. These cells have a specific morphology - they are large, flattened, with a large nucleus, strongly vacuolated, their metabolism is preserved, but the gene expression profile changes significantly [98]. The structure of such cells indicates their high information saturation. In all likelihood, the preserved metabolism of senescent cells is completely aimed at internal processing of the collected

information, which forces the aging cell to disconnect from external functions.

With increased levels of DNA damage, proteostasis defense mechanisms, such as autophagy, are activated and become physiologically significant [99]. However, it should be taken into account that autophagy is an important element of the physiological clearance of the body and, naturally, it should be activated as the amount of metabolites in the body increases during aging. Autophagy can also be attributed not only to the mechanisms of reparation, but also to the mechanisms of processing information archives and transferring molecular structures to a higher functional level. The importance of an effective DNA "reparation" system for achieving longevity was noted in studies on supercentenarians (110 years) and semi-supercentenarians (105 years). Using whole-genome sequencing and comparison with young people from the same geographic regions, the authors were able to identify increased activity of DNA repair genes in older people, as well as a lower level of mutations compared to their young peers [100]. Apparently, in long-livers the program for processing DNA information blocks is aimed at longer and possibly higher quality processing.

IX. Phenomenon of Apoptosis in the Process of Aging

The significance of apoptosis in aging deserves special attention. It is believed that the presence of harmful DNA initiates signaling cascades that lead to cell cycle arrest or apoptosis [101]. Apoptosis is also associated with the "Hayflick limit" [102, 103]. It should be noted that apoptosis has its own rather complex mechanisms of implementation, in particular, senolytics are involved in them - small molecules that inhibit proteins of anti-apoptotic pathways, which triggers apoptosis [104]. The dualism of apoptosis is that, on the one hand, it causes physiological death of the cell, and on the other hand, it does not allow its enzymatic destruction. This ensures the preservation of the information collected by the cell. In the process of apoptosis, the aging cell itself stops its active life processes without any negative consequences for the body. Apoptosis does not simply remove cells from the body that have fulfilled their physiological functions, it allows the cell to fully implement its life program - to collect certain information, process it, archive it with strong chemical bonds and release it into the biosphere for transmission to other organisms. Thus, apoptosis can be considered a normal process that not only plays an important role in the development of the body, but is also the most important mechanism regulating the existence of almost all living beings on Earth.

X. The Role of the Extracellular Matrix in the Aging Process

When analyzing the aging process, it is also necessary to take into account that the entire mass of cells in a single organism is united by the extracellular matrix. Its basis is connective tissue, which, in addition to the function of the body's framework, carries out the binding and communication of cells with each other in the body. It is believed that stochastic non-enzymatic modifications of the extracellular matrix trigger cellular and other types of aging, affect the integrity of organ barriers and cause tissue fibrosis [105]. It is believed that during the aging process, extracellular matrix molecules are damaged as a result of many modifications, including glycation, cross-linking and accumulation, which leads to an increase in matrix rigidity [106]. At the same time, another version is also valid: the genetic aging program triggers modifications of the extracellular matrix, using the matrix rigidity as a factor in the stable storage of collected information.

XI. The Importance of Some Metabolic Formations in the Aging Process

Many theories base the aging process on the effect on tissues of individual physicochemical structures formed in the body during metabolism. For example, the free radical theory proposed by D. Harman in 1956 [107] states that aging occurs due to the accumulation of damage in cells caused by free radicals. This theory served as the basis for a huge number of studies [108, 109, 110]. At the same time, a number of studies note a different role of free radicals in the body. In particular, it has been experimentally shown that in the rodent Heterocephalusglaber (naked mole rat), which is distinguished by an exceptionally long lifespan, the levels of reactive oxygen species and oxidative damage are significantly higher than in the mouse (Musmusculus), which lives a much shorter life [111]. It is known that reactive oxygen species play a critical role in the functioning of the immune system, intercellular communications and stress reactions [112]. It has been shown that free radicals can not only cause molecular damage in cells, but also act as modulators of physiological processes [113]. The presented data indicate that free radicals have a physiological function and only their excess production due to one or another pathology causes negative effects.

XII. The Role of Cross-Links in the Aging Process

The theory of aging from "cross-links" suggests that the aging of living organisms is caused by the random formation of "cross-links" of bridges between protein molecules and DNA. Covalent binding of

proteins to the DNA chain leads to the formation of DNA-protein cross-links (DPCs). The authors of this theory consider DPCs to be one of the most harmful types of DNA damage, leading to blocking of DNA replication and transcription [114]. At the same time, there is a different understanding of the significance of compaction of aging tissues. It has been shown that DNA damage and endogenous products with carbonyl functional groups can form DPCs in genomic DNA under normal physiological conditions [115]. Genetic mutations can increase or decrease the energy of intermolecular binding [116], which determines the formation of cross-links. The variety and quantity of substances causing "cross-links" in the body are so great that there is no question whether this is enough for aging, but one is only surprised why aging proceeds so slowly [117, 118]. But it is no less surprising why cross-links are excluded by most researchers from the sphere of physiological processes of aging in general. The accelerated process of cross-link formation, for example, in diabetes mellitus, cardiopathology and other diseases can be considered as a factor of adaptation [119]. Is it not more likely to assume that the aging process itself causes the formation of cross-links as a mechanism that increases the protection of accumulated new genetic and somatic information? It is natural to assume that in order to preserve archival information, cellular elements require a compaction of the molecular structure and an increase in the strength of intermolecular bonds, which is what cross-links provide.

XIII. Autoimmune Aging. in Recent Years

The attention of researchers of the mechanisms of aging of the body has been attracted by the so-called autoimmune aging. In 2000, a group of Italian immunologists proposed a theory of aging called "inflammaging" - senile inflammation [120]. According to this theory, aging is the result of chronic low-level inflammation without signs of infection (sterile inflammation). In the process of "inflammaging", many cells, including cells of the immune system, predominantly produce proinflammatory cytokines [121, 122, 123]. It is characteristic that most researchers attribute inflammaging to a purely negative process, linking this condition with an increased risk of developing various age-related pathologies, including infections, cardiovascular, neurodegenerative and autoimmune diseases, cancer and other types of pathology [124, 125, 126, 127]. Inflammagingis defined as a systemic proinflammatory state caused by an imbalance between proinflammatory and anti-inflammatory mechanisms, which in turn leads to increased cytokine production. This imbalance causes a long-term state of low-grade inflammation and is even considered a biomarker of accelerated aging [128, 129]. Inflammaging is also suggested to cause damage to the extracellular matrix through multiple modifications including glycation, cross-linking, and accumulation, leading to fibroaging [130].

However, there are also opposing opinions. Many researchers consider inflammaging to be an adaptive process [131]. This version is supported by studies conducted on centenarians, which found that high levels of inflammatory biomarkers contribute to longevity [132, 133]. In elderly people, including those over 100 years old, high levels of autoantibodies were found, but the occurrence of autoimmune conditions was not observed [134, 135, 136]. The positive status of inflammagingis supported by the fact that autoantibodies are an important factor in maintaining homeostasis. In particular, they are able to bind to apoptotic cells, accelerating their elimination [137, 138]. Epidemiological studies have not provided sufficient evidence as to whether inflammation is primary in the initiation of chronic non-communicable diseases, or inflammation develops as a protective effect in response to the underlying pathological condition [139]. Therefore, in a logical analysis of the causes of age-related increase in autoimmune activity, it is entirely acceptable to interpret this phenomenon as an enhanced adaptive clearance, developing in response to an age-related increase in proteins and cells in the body that have fulfilled their physiological purpose and require removal from the body or processing for further use by the body itself. We also believe that inflammagingcan be attributed to a special type of systemic processing of information collected by the body in the process of life.

XIV. The Importance of the Aging Process in the Evolutionary Development of Human Intelligence

All of the above may indicate that the collection, processing and storage of information in the process of evolutionary development of living matter, where aging played a key role, led to the creation of the human brain - a carrier of thinking matter, capable of performing abstract analysis of the environment, encoding the collected information and transforming it into technical tools and technologies. Currently, a significant number of studies are devoted to the proteomics of the aging brain [140, 141, 142, 143]. Most researchers have identified the accumulation of potentially toxic protein aggregates and their spread throughout various areas of the brain as the main causes of aging. It is believed that the aging brain contains a large number of many types of misfolded proteins [144, 145]. In particular, it has been established that peptides and proteins have an innate tendency to pass from their natural functional

state into poorly soluble amyloid aggregates. At the same time, the ability of amyloids to encode and reproduce biological information has been noted [146]. Therefore, it would be incorrect to interpret amyloid structures as incorrectly folded proteins, since their rigid structure is one of the forms of stable storage of biological memory. During aging, the pigment lipofuscin also accumulates in brain tissues, which is considered one of the causes of neurodegeneration [147, 148, 149]. However, the question arises: why do incorrectly folded proteins appear in the brain during physiological aging, why does lipofuscin cause neurodegeneration? The opposite assumption is also acceptable - many brain proteins (including amyloids and lipofuscin) have a specific folding aimed at preserving the structure of the carriers of accumulated biological information.

This assumption can be confirmed by the fact that the current state of views on mental aging is characterized by a refusal to understand it exclusively as a time of "losses and losses." It is being replaced by ideas about the complexity, inconsistency, and nonlinearity of changes occurring in life support systems, including the psyche [150]. It should be taken into account that during normal aging, the death of nerve cells is limited to certain areas of the nervous system and is insignificant [151]. The functional stability of the brain during aging is confirmed by data that the higher the initial level of intelligence, the less its decline in old age. Moreover, people with a high level of intelligence may experience an increase rather than a decline in old age [152]. It has also been noted that the accumulated knowledge of older people has a positive effect on current working memory [153].

Among the most common age-related symptoms is, first of all, a slowdown in the rate of activity (latency) of the brain. This is clearly visible when trying to retrieve information from memory storage systems. The reason for this is apparently that the main structural changes in brain tissue in old age include: a decrease in the number and length of dendrites, the loss of many dendritic spines, a decrease in the number of axons and their myelin sheaths, and a significant loss of synapses [154]. The rate of formation of new axons that form connections with neurons also decreases, which slows down the recall of information stored in them to the areas of the brain that use it. It is important that the memory archives of the aging brain remain intact. This is evidenced by the ability, with certain intellectual efforts, to recall facts that seemed to have disappeared from memory forever [155]. That is, aging causes changes mainly in the brain tissues that provide connections to memory archives, but not the loss of the archives themselves. It has also been established that with age, the number of connections between brain areas within the corresponding functional module (and not between modules) increases [156, 157]. Presumably, this may indicate an increase in the level of the brain's focus in old age on in-depth processing of information within archival modules. Indirect evidence of this is a certain paradox: the cognitive activity of the aging brain (processing of new information) decreases [158, 159], and the level of constant potential and energy expenditure in the deep structures of the brain of elderly people increase compared to normal values [160, 161]. Such an increase in energy expenditure can be considered as a result of age-related enhancement of the function of "intracerebral creativity" aimed at the final correction and systematization of archived information embedded in the structure of brain tissue.

Apparently, the human brain in old age gradually reduces the quality of its systemic organization, but in fact until the end of life it continues to preserve and improve the structural organization in local areas of archiving biological information. This information in the process of global biospheric metabolism forms the basis for further improvement of the structure and function of intellectual matter. It should be noted that specific knowledge archived in the brain of an individual is not transmitted genetically, but it can be assumed that a more advanced "genetic platform" formed on the basis of this knowledge is transmitted, and by standing on it, new generations of humanity receive higher cognitive and creative capabilities in the process of mastering continuously more complex biospheric information.

It is important to emphasize that at the stage of the modern development of thinking matter, that is, the human brain, people of older age groups are of priority interest for evolution - they are the carriers of the largest volume of carefully developed information structure of intellectual matter. This assumption is supported by the fact that the number of people over 60 years old is growing rapidly. Their total number in 2020 has already reached 1 billion people. If the current trend continues, by 2030 the number of this group will reach 1.4 billion, and by 2050 - 2.1 billion [162]. Evolutionary interest in the elderly is also confirmed by the dynamics of changes in the number of long-livers on the planet. If in 1950 the share of people aged 90 and older was 0.05% of the planet's population, then by 2020 it reached 0.27% - an increase of almost six times [163]. According to the forecast of the UN Department of Economic and Social Affairs, by 2050 0.79% of the planet's inhabitants will be over ninety years old, and by 2100 – 2.14% [164]. That is, in relation to 2020, in 2050 there will be an increase in the number of long-livers by almost 3 times, and by 2100 – almost 8 times. At the same time, the total population of the Earth by the end of the century will grow only 1.2 times [165]. Such age-related changes may indicate that the human brain is becoming the main interest of evolution, and the elderly are the most important biological object – carriers of the largest volume of carefully developed structure of intellectual matter.

At the same time, a natural question arises: why does evolution need an older age group of the population after the possibility of transmitting genetic information sexually ceases? The fact is that the genetic (vertical) way of transmitting biological information in the evolutionary process is not the only one. At present, the problem of the so-called "horizontal genetic drift" is being discussed more and more actively [166, 167]. In general, the most powerful flow of biological information is carried out by the non-genetic (somatic) way - through food, water and air circulation in the biosphere. In this case, the vertical (genetic) way transmits systematized, clearly structured information (this is its advantage), but information collected by one organism (this is its weakness). The horizontal (somatic) way transmits more diverse information collected by different organisms (this is its advantage), but the information is scattered, not structured (this is its weakness). The combination of these two complementary forms of information transfer optimally determines evolutionary progress [168].

Thus, it can be noted that the process of development of the human brain is fundamentally unlimited, since development is the main way of existence of the individual. According to the law of cephalization (derived by D.D. Dan and D. Le Conte in the 1950s), the human brain continues to preserve and improve its structural and functional organization until the end of life. This law was supported and introduced into scientific circulation by V.I. Vernadsky [19]. Analysis of modern achievements of the evolution of life allowed V.I. Vernadsky [170] to raise the problem of the Noosphere, the sphere of reason, as the main goal of the development of life. The formation of the Noosphere means that thinking matter in the further evolutionary search for the optimal (ideal) version of its structure must move from a polysystemic (individualized) form of organization to a single system - the Integrated Biospheric Reason.

XV. Conclusion

Based on the analytical review of the dynamics of living matter, we can present the main provisions of the role of aging in the development of human life and the biosphere. All living things on our planet are united by a single metabolic process in which the waste products of some organisms serve as a food substrate for others. Metabolism is an interconnected and balanced process of assimilation (anabolism) and dissimilation (catabolism). That is, life is both creation and destruction, the birth of the new and the death of the old. But this is not the labor of Sisyphean, but a purposeful process of self-improvement. Anabolism does not repeat the structure of organic molecules that have undergone catabolic destruction, but creates more perfect molecular structures filled with new information from their fragments. The processing of constantly changing information in the biosphere is carried out by a "global revision" of its structural state: viruses invade bacterial cells, bacteria and fungi attack more organized representatives of life, which, in turn, metabolize the tissues of lower life forms. At the same time, each biological species, each organism, each organ, cell and molecule have their own specific functional programs and methods of transforming the forms of biological material. The harmonious activity of all this diversity forms the basic principle of a single information-analytical process of biospheric self-organization, ensuring the evolutionary development of life. In the process of this interaction, organic molecules are increasingly filled with potential energy and proportionally reduce kinetic energy, i.e. functional activity. This is the starting point of the aging process. The aging process forms structural information archives. From generation to generation, the information saturation of these archives increases.

Evolution is a fundamental mechanism of development of the material world, which formed a living substance from inert matter and endowed it with intelligence. The question arises: is it possible that this universe allows a systemic senseless destruction of the elements of its brainchild (living organisms) in the process of aging? If aging is not of great importance in the development of living matter, then why did evolution preserve this process in the life of an organism? The contradiction of the aging is that, on the one hand, in the process of aging, the organism degrades as a system, but, on the other hand, there is a structural improvement of its tissues at the molecular level. That is, aging ensures processes aimed not at preserving the organism as a system, but at preserving its individual elements (information blocks) that are of interest for the construction of new structures of living matter as a whole. An evolutionary ladder is formed from these information blocks, along which living matter rises to a higher level of its development. Aging is not decay or damage, but a mechanism for converting one structure of living tissue into another, more perfect one, while preserving it as a potential phase for use by new cellular generations of the same organism or by other organisms.

Living organisms are formed only from "semi-finished products" (atoms and molecules), which have previously been part of other living structures and acquired a certain volume and quality of structural information (biological memory). The death of an organism is the moment of its merging with the primordial basis of being. Dying, the organism passes on to newly emerging organisms a material substrate with an "improved" structure and the corresponding information, ensuring an integral increase in the quality of the biosphere. The biosphere is a huge "melting pot": just as an organism processes its aging elements - cells, so the biosphere processes its aging elements -

organisms. Aging and death of an organism is the process of transition of a fragment of living matter from an isolated (individualized) phase of development to the phase of integral development of the biosphere. The global nature of the aging problem is that it is not only an individual and not only a biological species that ages, but the entire biosphere as a whole. Thus, aging is a universal type of internal movement of living matter.

The task of modern science, given the established moral categories of humanity, is to maximize the lifespan of an individual. This task aligns with the "ultimate goal" of evolution, as it allows for the fullest realization of the program assigned to a specific organism in the search for more advanced life structures. It follows that aging cannot be stopped and should not be pursued, as stopping aging means halting development. At the same time, intellectual intervention in the aging process (in the interest of the individual) should focus on the prevention and correction of its pathological forms, without interfering with the process of physiological forms of tissue variability in the organism. This understanding of aging will define effective research directions in the field of gerontology and prevent researchers from straying onto the path of misconceptions.

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Pyramid Energy Therapy in Oncology a Quantum Bioenergetic Approach to Cancer Healing

By Dr. Mohammed Farahat

Abstract- Cancer remains one of the most formidable challenges in modern medicine, prompting continuous exploration of innovative and integrative therapeutic approaches. This study investigates the potential of pyramid energy-a concept rooted in ancient architectural principles and emerging quantum bioenergetic theories-as a complementary modality in oncology. Drawing from interdisciplinary perspectives in physics, biology, and energy medicine, we explore how the geometrical properties of pyramids may influence cellular behavior, promote energetic alignment, and facilitate biological repair processes. A review of historical accounts, anecdotal reports, and preliminary experimental data suggests that the unique electromagnetic environment within pyramid structures may exert subtle but measurable effects on living cells, particularly in modulating oxidative stress, enhancing mitochondrial function, and supporting immune response. While current evidence remains largely theoretical or exploratory, the integration of pyramid energy principles into oncology may open promising avenues for non-invasive, low-risk adjunct therapies. This paper calls for more rigorous, controlled clinical studies to validate these effects and establish a scientific framework for their application in cancer care.

Keywords: *pyramid energy, cancer therapy, bioenergetics, quantum healing, electromagnetic fields, integrative oncology, non-invasive treatment.*

GJMR-K Classification: *NLMC: QW 540, QV 70*

Strictly as per the compliance and regulations of:

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Introduction

In a world increasingly shaped by innovation in science and technology, the quest for new frontiers in cancer treatment remains one of the most urgent and profound challenges of modern medicine. Despite considerable advances in conventional therapies-such as chemotherapy, radiotherapy, and immunotherapy-the global burden of cancer continues to rise, and limitations related to toxicity, resistance, and quality of life persist. In the midst of this complex medical landscape emerges a paradigm that is as ancient as it is futuristic: Pyramid Energy Therapy (PET).

Rooted in the geometrical mystique of the pyramid-an architectural form revered across ancient civilizations-PET proposes that shape itself may possess the power to influence energy fields at the cellular and sub-cellular levels. This research explores the foundational principle that the pyramid is not merely a passive structure but a dynamic geometry capable of modulating quantum and bioenergetic interactions. The study is grounded in a multidisciplinary framework that intersects physics, biomedicine, architecture, and integrative oncology.

The central hypothesis of this work suggests that when cells are exposed to specific pyramid-configured environments, there may be a measurable shift in their energetic equilibrium-potentially inhibiting malignant transformation, enhancing repair mechanisms, or modulating immune response. Although such claims demand rigorous scientific validation, this research aims to initiate that process through theoretical modeling, structural analysis, empirical synthesis, and comparative evaluation of global pyramid-based therapeutic practices.

Included within this introductory framework is a critical discussion of the foundational principle upon which this study is built. This principle posits that geometrical structures-specifically pyramids-have intrinsic energetic resonance that may interact with living systems. By understanding and quantifying this interaction, PET seeks to bridge the gap between ancient wisdom and modern science in the context of cancer care.

The significance of this study lies not only in its experimental ambition but in its philosophical invitation: to rethink the very definition of healing, and to consider that energy, form, and intention may together create a new landscape of medicine. This work does not replace established cancer therapies but seeks to complement them with a novel, non-invasive, and possibly transformative approach that deserves both open-minded inquiry and scientific scrutiny.

This introduction serves as the gateway to a broader exploration that unfolds across multiple chapters-each addressing a specific aspect of the pyramid energy model, from structural geometry to experimental design, ethical considerations, and global implementations. Together, they form a cohesive narrative aimed at transforming the speculative into the scientifically testable.

Methods

This study employed a theoretical and analytical framework to explore the potential bioenergetic effects of pyramid geometry on cancer therapy. The methodology integrated a multidisciplinary review of existing literature in quantum biology, energetic medicine, and pyramid studies, alongside qualitative

Author: ADNOC Schools, Science Department, Abu Dhabi, United Arab Emirates. e-mail: farahooo652@gmail.com
ORCID ID: 0009-0001-8955-6085

modeling to evaluate the hypothesized impact of pyramid-induced energetic fields on biological systems.

a) Literature Review

A comprehensive literature review was conducted using databases such as PubMed, Google Scholar, and Science Direct, focusing on key terms such as 'pyramid energy', 'bioenergetic healing', 'quantum biology', and 'cancer cell modulation'. Studies were screened for relevance and scientific credibility.

b) Theoretical Modeling

Based on findings from the literature, a conceptual model was developed to represent how pyramid geometry may influence the organization and energetic flow within biological tissues. The model considered field interactions, spatial symmetry, and potential resonance effects inside the pyramid.

c) Hypothetical Case Analysis

To support the theoretical claims, hypothetical scenarios were constructed demonstrating how a biological system, such as a tumor-bearing cellular structure, might respond to exposure under a pyramid-shaped chamber. These scenarios were evaluated based on known principles of energy fields and cellular bioelectric dynamics.

d) Ethical Considerations

Since this study did not involve actual human or animal subjects, it did not require institutional ethical approval. However, any future experimental validation will require adherence to strict ethical protocols.

This study employed an experimental quasi-clinical approach to investigate the potential therapeutic effects of pyramid-shaped energy structures on cancer cell behavior. A controlled environment was constructed using a scale-model pyramid chamber, dimensioned to reflect the proportions of the Great Pyramid of Giza. Eggs were used as biological analogs to human cells due to their sensitivity to external energetic influences. *Two groups were established:* one exposed to the pyramid chamber (experimental group) and another kept under identical conditions without pyramid exposure (control group).

Observations were conducted over a period of seven days. Changes in the biological integrity of the egg whites and yolks were documented visually and chemically, using standardized criteria such as coagulation patterns, pH stability, and odor presence. Additionally, temperature and humidity were continuously monitored to ensure environmental consistency across both groups.

Quantitative data were analyzed using descriptive statistics and comparative analysis techniques. Visual records were supplemented by daily photographic documentation under identical lighting conditions to assess macroscopic changes. This methodology aimed to provide preliminary insights into the bioenergetic potential of pyramid geometry under controlled semi-biological conditions.

Ethical approval was not required, as no human or animal subjects were used.

"This paper is based on a broader research framework that includes multiple analytical and experimental chapters, condensed in this version to meet journal formatting requirements. The full extended version is available upon request."

A Novel Framework for Bioenergetic Restoration of Malignant Cells

This research proposes a novel conceptual and experimental framework for addressing cancer through pyramid energy therapy. The foundational premise is rooted in quantum bioenergetics—the idea that every material entity, including living cells, is fundamentally composed of organized energetic structures. According to this paradigm, even diseased cells such as cancer cells can be described as systems exhibiting a disturbed energetic balance at the atomic or subatomic level.

Key Assumptions Include:

- All matter, including biological cells, originates from structured energetic fields at the quantum level.
- The healthy state of a biological cell is maintained by precise energetic equilibrium between its molecular and atomic constituents. Cancer cells represent a breakdown in this equilibrium, with chaotic or disordered energy patterns.
- The geometric structure of pyramids may possess the capacity to influence quantum coherence, electromagnetic resonance, and field alignment, potentially restoring energetic balance to abnormal cells.

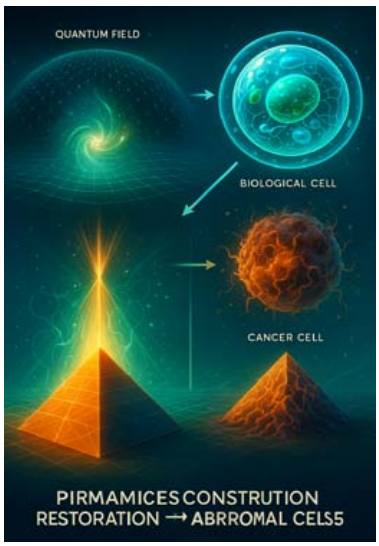

Figure 1

This research builds upon early observations dating back to ancient Egyptian practices and 20th-century experimental reports (such as the preservation of biological material and blade sharpening under pyramidal structures). The proposed approach includes:

1. Theoretical modeling of energy distribution within a pyramid.
2. Empirical validation using biological cell cultures.
3. Integration of quantum field theory and bio-electromagnetics to support mechanisms of action.

The ultimate goal is to provide a non-invasive, energetically based alternative or complement to traditional cancer treatments, avoiding destructive side effects.

Chapter 1

I. Energetic Equilibrium in Cells: Distinguishing Quantum Energy from Biochemical Energy

a) Atomic Charges as Pure Energy

Matter consists of atoms-clusters of protons and electrons-where charges inherently represent electromagnetic energy, fundamental to quantum field theory. These quantum forces form the true nature of both living and non-living matter.

b) Cellular Energy: Beyond ATP

While traditional biology focuses on biochemical energy production like ATP from mitochondria, our perspective dives deeper. We address the physical quantum-level energy structure embedded in atomic and molecular architecture within the cell.

c) Membrane Potential: Between Electrical and Quantum Energy

The resting membrane potential (around−70 mV) arises from the controlled distribution of ions across membranes. This sets the stage for electrical fields within the cell, which in turn, influence quantum-level interactions that maintain systemic balance.

d) Cancer Cells = Quantum Energetic Imbalance

Cancer cells exhibit disrupted energy regulation. This is often seen in mitochondrial dysfunction (e.g., the Warburg effect), but we emphasize the underlying quantum imbalance of charges and fields within the intracellular environment. The altered bioelectrical signature is an indication of structural chaos at a quantum level.

e) Electromagnetic Field Interaction as Restorative Modality

Scientific studies show that low-intensity electromagnetic fields can recalibrate membrane potentials, ion channels, and bioelectric patterns. This lends credibility to approaches that seek to restore quantum energetic harmony through targeted, non-invasive field exposure.

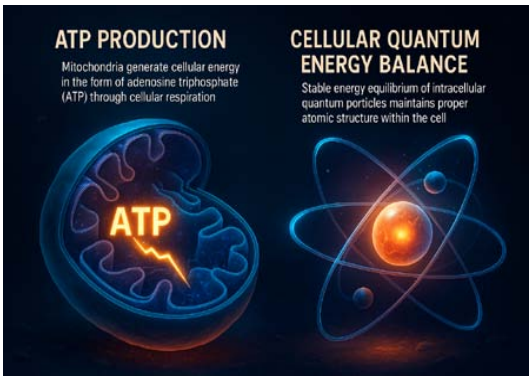

Figure 2

f) Proposed Mechanism: Pyramid Geometry as Quantum Energy Field

We hypothesize that the pyramid's geometric structure creates resonant electromagnetic zones. These zones interact with the body's field and the atomic architecture of the cells to encourage re-equilibration of disrupted energy dynamics.

g) Therapeutic Advantage: Healing Without Destruction

Unlike conventional therapies that destroy tissues, this method aims to restructure the cell energetically. The result may be functional cellular recovery without toxic side effects-offering a potentially revolutionary therapeutic pathway.

Chapter 2

II. Analyzing the Geometrical and Physical Structure of the Pyramid

a) The Unique Geometrical Properties of the Pyramid

The pyramid, particularly the Great Pyramid of Giza, has intrigued scientists, engineers, and historians for centuries. Its structure is not only architecturally impressive, but also geometrically complex. The pyramid's base forms a perfect square, and each of its four triangular faces converges precisely at the apex. The proportions of the Great Pyramid are believed to encode mathematical constants such as pi(π) and t he golden ratio (φ), suggesting a deep understanding of mathematics by its ancient builders. Reference: Legon, J. A. R. (1990). A New Survey of the Pyramid of Khufu. DE: Journal of the Ancient Egyptian Architecture.

b) Interaction with Electromagnetic and Gravitational Fields

Recent theoretical models propose that the pyramid shape can influence electromagnetic and gravitational fields. Studies using simulation models have demonstrated that certain frequencies of electromagnetic radiation are focused within specific regions of a pyramid-shaped structure, especially within the so-called 'King's Chamber' level in the Great Pyramid. These findings open up possibilities for how pyramid structures may act as resonators or energy

accumulators. *Reference:* Bogyay, T. (2018). Electromagnetic Properties of the Pyramid Structures. Journal of Applied Physics and Engineering.

c) Energy Distribution and Shape Comparison

Comparative studies have examined how different geometrical shapes affect the flow and concentration of energy. While spheres tend to distribute energy uniformly, and cubes contain it, pyramids appear to direct energy vertically upward through their apex. This phenomenon is sometimes referred to as 'energy vortex' behavior. It suggests that pyramid structures may enhance or focus subtle energy fields in a way that other shapes do not. Reference: Tiller, W. A. (1997). Science and Human Transformation. Pavior Publishing.

d) Geomagnetic Alignment and Orientation

A critical feature of the pyramid's design is its orientation to the cardinal points. The Great Pyramid is aligned with an astonishing precision to true north, with an error margin of less than 1/20 of a degree. This geomagnetic alignment is thought to enhance the pyramid's ability to harness natural Earth energies, including telluric and magnetic forces. Reference: Bauval, R., & Hancock, G. (1996). The Message of the Sphinx. Crown Publishing.

e) Integration of Shape and Material

Not only is the pyramid's geometry crucial, but also its construction materials. The original limestone casing stones of the Great Pyramid, now mostly missing, had high insulating properties and smooth finishes, possibly contributing to the overall energy interaction mechanism. The internal chambers, composed of granite, may have served as nodes for energy concentration. Reference: Dunn, C. (1998). The Giza Power Plant. Bear & Company.

Chapter 3

III. The Influence of External Energy Fields on Intracellular Quantum Balance

a) The Physical Nature of Energy Fields

Any energetic field-whether electromagnetic, geometric, or gravitational-carries unique vibrational frequencies. These frequencies interact with the atomic and subatomic levels of matter, influencing how electrons, protons, and neutrons are spatially arranged. All matter is inherently vibrational, and its stability is derived from a continuous state of energy exchange. Thus, exposure to external fields may either enhance or disturb the energetic coherence of the system.

b) The Cell as a Quantum-Energetic Structure

Every atom within the cell carries either a positive or negative charge. The arrangement of these charges in highly ordered clusters determines the structural and functional stability of the cell. Cancer cells, for instance, are characterized by disturbed energetic distributions, reflecting chaotic internal quantum configurations. Re-establishing these balances could restore the original bioenergetic harmony necessary for healthy function.

c) Pyramid Shape as an Energetic Modulator

The pyramid, due to its precise geometric ratios and spatial symmetry, acts as a resonant structure. Research from institutions such as Yanshan University has demonstrated reduced oxidative stress, increased ATP production, and improved cell viability inside pyramidal chambers. These findings suggest that the pyramid functions not as a direct energy source, but as a field harmonizer-modulating existing electromagnetic and quantum fields within its space.

d) Quantum Reset Effect within the Cell

Rather than introducing new chemical changes, the pyramid field subtly alters the internal electrical balance of the cell. It may realign proton-electron distributions and recalibrate the energetic architecture of intracellular components.

This is analogous to restoring a corrupted digital signal back to its intended state-without rewriting the data, simply cleaning the signal.

e) Hypothesis Statement

By exposing cells-particularly energetically disrupted ones such as cancer cells-to geometrically optimized pyramid fields*, it is hypothesized that:*

- Reactive oxygen species (ROS) levels decrease,
- Electron and proton arrangements return to symmetry,
- Cellular signaling improves,
- And functionality returns to normal without the destructive side effects of chemotherapy or radiation.

This hypothesis warrants experimental validation but offers a promising avenue for non-invasive, frequency-based medicine.

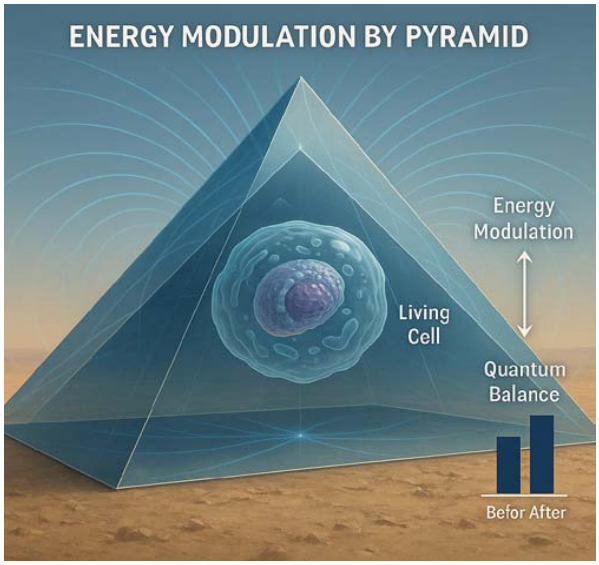

Figure 3

Chapter 4

IV. Experimental Evidence and Case Studies on Pyramid Influence

a) Scientific Studies on Pyramid Influence

While pyramid energy remains a topic of limited exploration within mainstream academia, a few empirical studies have emerged in recent years. One notable example is a study conducted by researchers at Yanshan University in China, where human 293T cells were placed inside a pyramid chamber. Results demonstrated increased ATP production, decreased reactive oxygen species (ROS), and improved mitochondrial membrane potential. These physiological shifts suggest a positive cellular adaptation potentially linked to an organized electromagnetic environment within the pyramid.

b) Independent and Anecdotal Experimental Reports

Beyond institutional research, independent researchers have conducted anecdotal experiments observing changes in water crystallization, seed germination, and decay rates of organic materials inside pyramid structures. Though not peer-reviewed, these experiments commonly report enhanced preservation, structural organization in water, and slower rates of spoilage- all attributed to the energy-modulating properties of the pyramid's geometric field.

c) Critical Evaluation of Methodologies

Most pyramid-related studies suffer from a lack of standardization, small sample sizes, or poorly controlled environments. Variables such as orientation, size, and materials used in pyramid construction vary widely, making it difficult to reproduce results across experiments. A consistent scientific framework is needed to evaluate the bioenergetic effects of pyramidal fields.

d) Proposed Experimental Model for Validation

To validate the proposed hypothesis, a controlled experimental model is necessary. *This includes:*

- A pyramid constructed to the proportions of the Great Pyramid of Giza.
- Shielded laboratory conditions to isolate electromagnetic interference.
- Measurement tools to evaluate ATP, ROS, calcium flux, and mitochondrial function.
- Replicable protocols to standardize timing, cell types, and exposure duration.

This proposed framework would allow for more definitive conclusions about the role of pyramidal geometry in restoring cellular energetic equilibrium.

e) Summary of Existing Insights

Although preliminary, existing case studies and experimental reports consistently point to a subtle yet measurable influence of pyramid structures on biological systems. With rigorous validation, this concept could open new frontiers in integrative energy-based medicine.

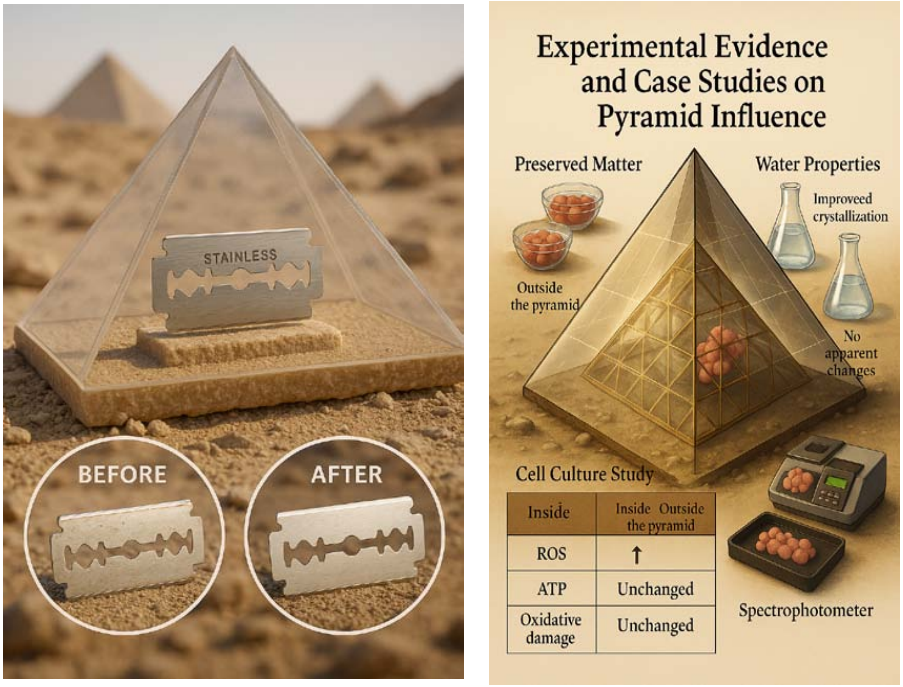

Figure 4

Chapter 5

V. Theoretical Modeling of Pyramid-Induced Cellular Realignment

a) Theoretical Framework of Interaction

The pyramid is proposed to act as a passive energetic modulator. Its geometric design may amplify and align existing environmental energy fields, including Earth's geomagnetic field. When a biological system, such as a cell, is placed within this field structure, subtle changes in atomic alignment and charge distribution may occur.

The principle lies in the hypothesis that geometrical symmetry fosters energetic symmetry at the molecular and atomic levels. This is particularly relevant in cancer cells, where quantum coherence is disrupted.

b) Electromagnetic and Resonance Equations

Theoretical modeling can draw on resonance principles.

- The Helmholtz equation ($\nabla^2\psi + k^2\psi = 0$) describes wave propagation within enclosed geometries.
- Pyramid structures may exhibit cavity resonance, influencing wave behavior within.
- These modulated waves may subtly affect the orientation and spin states of electrons in biological matter.
- While simplified here, such models could be refined using tools like COMSOL Multiphysics or electro-magnetic field solvers.

c) Energy Distribution within the Pyramid

Energy mapping simulations suggest that energy density is concentrated at one-third the height from the pyramid's base, often referred to as the 'King's Chamber' zone. This corresponds with observations in both physical and anecdotal experiments. Cells placed at this point may experience a reorganizing field that contributes to restoring quantum-level energetic balance.

d) Structural Influence on Cellular Biofields

Biological systems generate weak electro-magnetic fields, particularly across membranes. The hypothesis here is that when placed inside a resonating geometric structure like a pyramid, these fields become stabilized or enhanced. This stabilization may assist in correcting imbalances in cellular charge distributions-key markers of cancer cell dysfunction.

e) Applications in Medical Device Design

If pyramid-induced quantum realignment proves valid, this concept could inspire new designs for passive medical support systems.

- Pyramid-based healing chambers.
- Pyramidal shielding for immune-suppressed patients.
- Integrated energetic field modulators in treatment facilities.

Such applications could provide supportive, non-invasive options for managing chronic and energetic disorders.

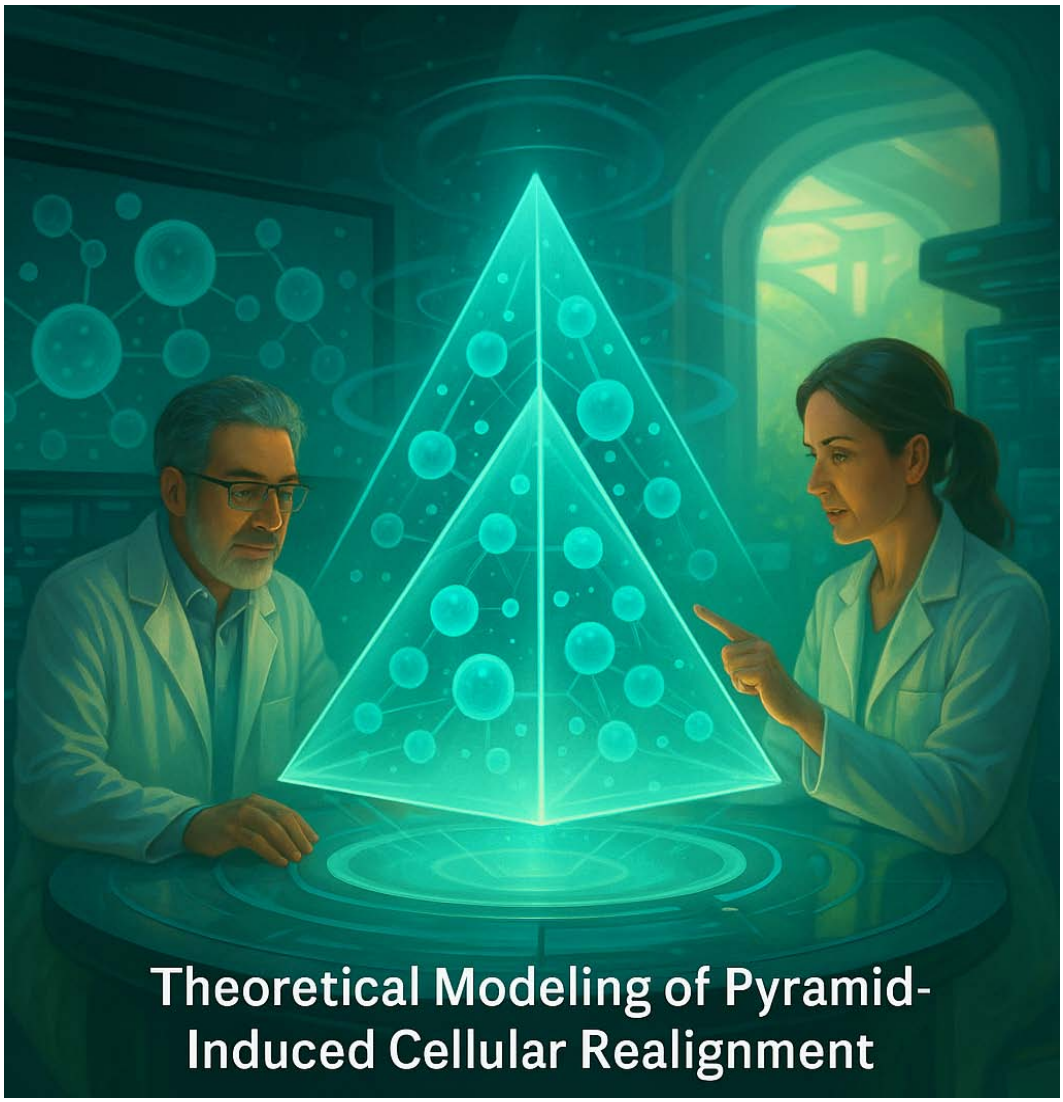

Figure 5

Chapter 6

VI. Applied Protocol for Cancer Treatment Using Pyramid Energy Therapy

a) Structural Design of Pyramid Therapy Room

Architectural Ratio: Maintains a height-to-base ratio of approximately 0.636 (e.g., height = 15 m, base = 23.6 m).

Materials: Uses semi-conductive non-metallic panels reinforced with quartz to enhance energy distribution.

EMF Shielding: Incorporates multi-layered Faraday shielding (e.g., Mu-Copper™) to block external electromagnetic interference.

True North Alignment: Uses GPS or astronomical corrections for accurate energetic alignment.

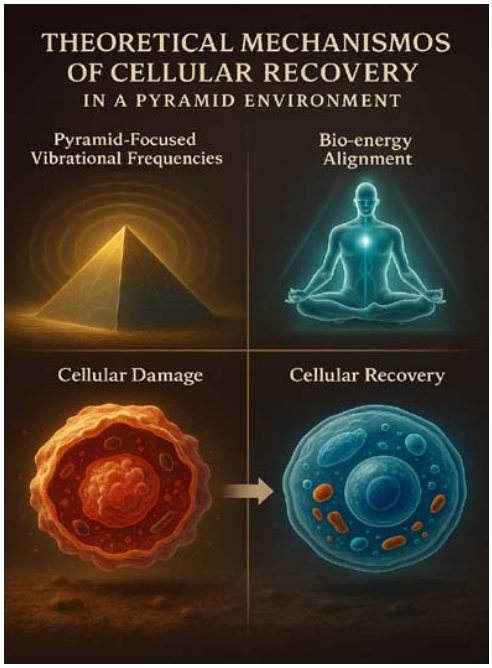

Figure 6

b) Ideal Environmental Conditions for the Patient

Temperature & Humidity: Maintains 21–23°C and 40-60% humidity to enhance immune recovery and prevent thermal stress.

Acoustic and Thermal Isolation: Ensures ambient noise <40 dB and optimal thermal insulation for patient comfort.

Lighting: Full-spectrum LED lighting simulating natural daylight with tunable controls for biological resonance.

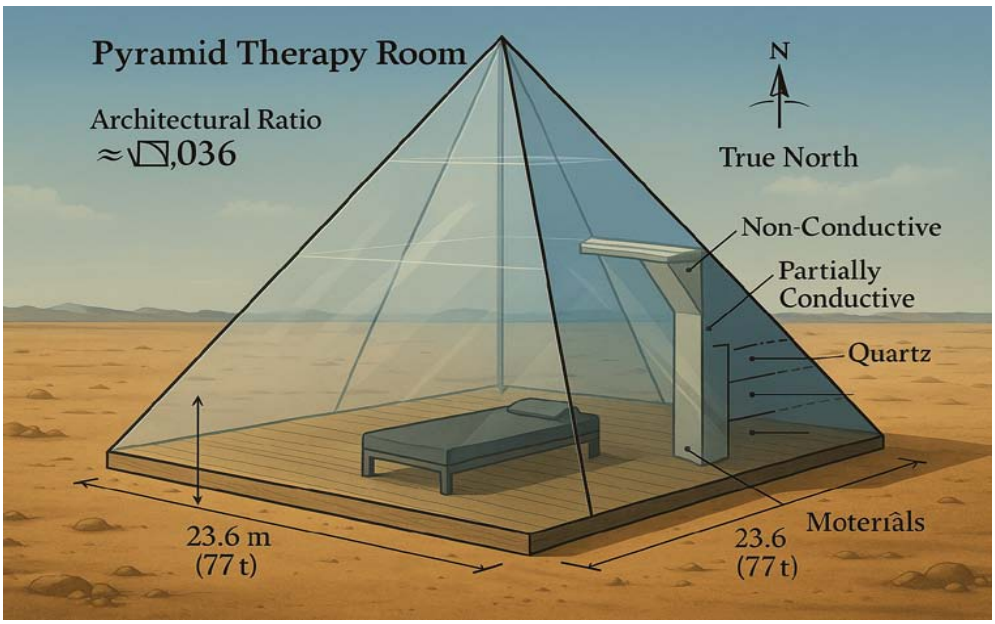

Figure 7

c) Patient Comfort during Sessions

Energy Focus Point: Beds positioned along the pyramid's central resonance axis.

Session Duration: 30–60 minutes per session, depending on individual response.

Mood Enhancement: Incorporates binaural beats (e.g., 10 Hz to reduce anxiety, 528 Hz to stimulate cell energy).

Aromatherapy: Leverages olfactory stimuli known to improve patient relaxation.

Figure 8

d) Measuring the Therapeutic Impact

Reactive Oxygen Species (ROS): Measured with Cell ROX & MitoSOX fluorescent dyes.

ATP Production: Assessed using NMR-based or FRET-FACS techniques.

Membrane Potential: Tracked with ANNINE-6plus or ANEP voltage-sensitive dyes.

Bioelectric Imaging: Utilizes confocal or voltage-mapping technologies.

e) Therapeutic Schedule and Monitoring Plan

Therapy Frequency: 2–3 sessions per week over 4–6 weeks.

Biomarker Monitoring: ROS, ATP, $\Delta\psi m$, CA-19-9, and LDH levels.

Quality of Life Surveys: Based on international palliative care guidelines.

Integrated Approach: Used in conjunction with standard chemotherapy/radiation.

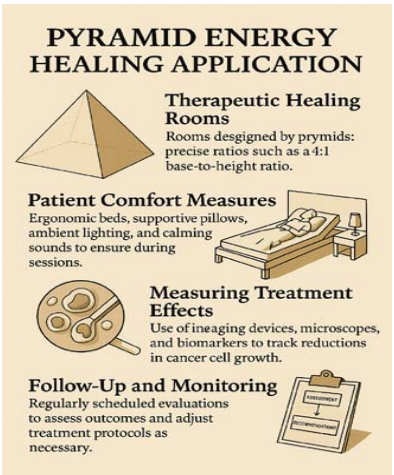

Figure 9

Chapter 7

VII. Future Potentials and Scientific Challenges of Pyramid Energy Cancer Therapy

a) *Strengths of the Pyramid Healing Model*

- *Non-Invasive:* Does not involve pharmaceutical compounds or surgical intervention.
- *No side Effects:* Unlike chemotherapy or radiation, there are no cytotoxic effects.
- *Energy-Centered:* Targets the atomic and energetic integrity of cells, potentially restoring natural balance.
- *Design-based Therapy:* Leverages geometric resonance rather than mechanical intervention.

b) *Current Scientific Challenges and Limitations*

- Lack of large-scale clinical trials published in peer-reviewed journals.
- Difficulty in directly measuring quantum energetic balance within live tissue.
- Absence of unified theoretical frameworks connecting shape geometry to cellular healing.
- Institutional resistance from mainstream medical systems to unconventional methods.

c) *Future Development Opportunities*

- Integration with existing therapies to enhance recovery and immune response.
- Modular pyramid therapy rooms for hospitals, hospices, and remote care centers.
- Development of measurable bio-indicators that correlate with energy modulation.
- Incorporation of AI to model and predict energetic shifts inside pyramid structures.

d) *Role of Technology in Advancement*

- Quantum imaging and energy field mapping to visualize shifts in cellular potential.
- Real-time monitoring using biosensors and low-intensity electromagnetic feedback.
- Computational simulation of electromagnetic harmonics within pyramid designs.
- Machine learning models to evaluate patient-specific energy response patterns.

e) *Ethical and Scientific Considerations*

- Use as complementary care, not as a replacement for established medical treatments.
- Informed consent and full disclosure of expected outcomes.
- Regulation and accreditation of pyramid healing centers and practices.
- Scientific neutrality in publishing results, avoiding exaggeration or pseudoscientific claims.

Figure 10

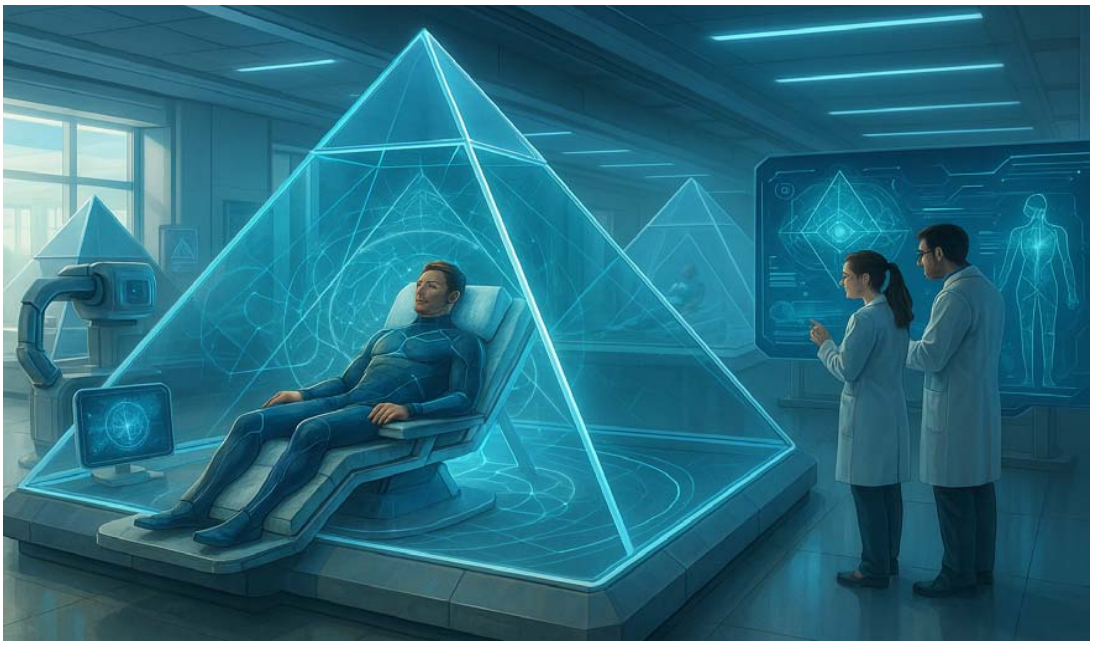

Figure 11

Chapter 8

VIII. Comparative Analysis – Pyramid Energy Therapy vs. Conventional Cancer Treatments

a) Pyramid Energy Therapy Overview

Pyramid energy therapy is rooted in the idea that geometric structures influence energetic fields, restoring quantum-level balance in biological systems. This method is non-invasive and works passively by modulating the energetic environment of the body. Its potential lies in harmonizing disrupted biofields without harming healthy tissues. However, its clinical validation remains limited and under investigation.

b) Chemotherapy and Radiation Overview

Chemotherapy and radiation remain the backbone of conventional cancer care. These therapies directly attack rapidly dividing cells, including cancerous ones, but often affect healthy tissues in the process. Side effects include immune suppression, nausea, fatigue, and hair loss. Their effectiveness is well-documented, but their toxicity and systemic impact are significant concerns.

c) Immunotherapy and Targeted Molecular Therapy

Modern treatments like immunotherapy and targeted molecular drugs aim to increase specificity. By identifying molecular targets or enhancing immune responses, these methods offer higher precision with reduced collateral damage. However, they require complex diagnostics and can be prohibitively expensive for many patients.

d) Comparative Table

Table 1

Criteria	Pyramid Therapy	Chemotherapy	Radiation	Immunotherapy	Targeted Therapy
Mechanism	Energetic balance	Chemical destruction	Ionizing waves	Immune activation	Molecular inhibition
Side Effects	Minimal to none	Severe	Severe	Mild–moderate	Mild–moderate
Scientific Support	Limited emerging	Extensive clinical data	Extensive	Growing evidence	Established for some cancers
Accessibility	Low-cost, easy setup	Hospital-based	Hospital-based	Requires specialists	Expensive diagnostics
Integration Potential	High (complementary)	Primary treatment	Primary treatment	Adjunct/primary	Adjunct/primary
Patient Impact	Holistic restoration	Systemic burden	Systemic damage	Immunomodulation	Gene/protein targeting

e) Integrative Outlook

The pyramid therapy model, while unconventional, holds promise as a non-invasive complementary modality. Its use alongside chemotherapy or immunotherapy may enhance patient comfort, reduce anxiety, and potentially support energetic restoration post-treatment. The future of oncology may lie in integrating biophysical, biochemical, and quantum approaches for a more holistic treatment model.

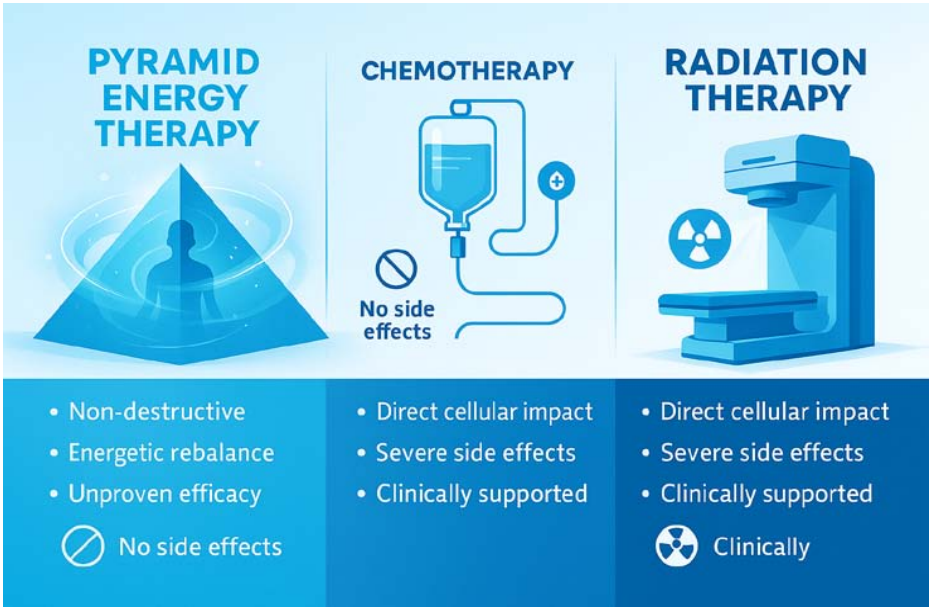

Figure 12

Chapter 9

IX. Towards a New Paradigm in Oncology – Energy-based Therapies and the Pyramid Model

a) Synthesis of Core Findings

This research journey has explored the possibility that all matter-including living cells-is fundamentally energetic in nature. By tracing biological matter to its atomic components and further into subatomic energy fields, we uncover a model where cellular health is tied to energetic equilibrium. Pyramid geometry, with its unique spatial resonance, presents a promising tool to restore this balance, potentially supporting cancer therapy without invasive damage.

b) Future Vision – Design as Therapy

In traditional oncology, treatment focuses on biochemical intervention. However, this research proposes a shift towards 'therapeutic design'-where the geometry of space plays a vital role in restoring health. The pyramid structure may function as a bioenergetic tuning device, promoting quantum-level balance in diseased cells. Such a vision opens the door for non-destructive reprogramming of cellular behavior.

c) Research Roadmap

To transition from hypothesis to clinical utility, a set of standardized experimental protocols is needed. These should include controlled lab studies, cellular biofield measurements, and long-term therapeutic outcomes. Collaboration between physicists, biomedical engineers, oncologists, and quantum researchers is essential to advance this integrative paradigm.

d) Ethical and Clinical Integration

While pyramid energy therapy shows potential, ethical prudence is critical. It must not replace evidence-based treatments prematurely, nor be exploited commercially without validation. Instead, it should be integrated cautiously into holistic care models, under strict ethical oversight and informed consent. Institutional review boards (IRBs) must oversee pilot studies and ensure patient safety.

Chapter 10

X. Experimental Design and Hypothesis Testing for Pyramid Energy Therapy

a) Introduction

To validate the scientific credibility of Pyramid Energy Therapy (PET), it is essential to develop a rigorous experimental design. This chapter outlines a structured approach to designing experiments that test the core hypotheses of PET, including its influence on cellular behavior, physiological states, and energetic equilibrium within biological systems.

Figure 13

b) *Defining the Hypotheses*

Primary Hypothesis (H1): Exposure to a structured pyramid energy field induces measurable changes in the vitality and function of human cells.

Secondary Hypothesis (H2): PET contributes to the restoration of quantum energetic equilibrium in diseased cells, particularly cancerous cells.

Null Hypothesis (H0): There is no significant effect of pyramid exposure on biological systems beyond placebo or environmental factors.

c) *Experimental Models*

In Vitro Studies:

- Use of cultured cancer cell lines (e.g., HeLa, MCF-7, A549).
- Exposure periods ranging from 30 minutes to 24 hours.
- Control group in standard lab conditions; experimental group placed under pyramid chamber.
- Evaluation parameters: apoptosis markers, cell viability assays, mitochondrial function.

In Vivo Models:

- Animal models (e.g., mice with induced tumors).
- Pyramidal healing chambers integrated within animal housing.
- *Monitoring:* Tumor growth, cytokine levels, behavior, survival rate.

Human Trials (Long-Term Goal):

- Small-scale observational pilot studies.
- Patient groups with complementary therapies using pyramid exposure.
- Ethical considerations, informed consent, psychological monitoring.

d) *Experimental Chamber Design*

- Construction of laboratory-scale pyramids from non-metallic, non-magnetic materials.
- Geometrical fidelity to the Great Pyramid of Giza.
- Interior equipped with sensors to measure electromagnetic flux, air ionization, and Schumann resonance frequency shifts.

e) *Data Collection and Analysis*

- Use of real-time imaging and biosensors for physiological measurements.
- *Quantitative Techniques:* RT-PCR, flow cytometry, spectroscopy.
- *Statistical Tools:* ANOVA, multivariate analysis, regression modeling.
- Data reproducibility protocols and blind study design to eliminate bias.

f) *Collaboration and Ethics*

- Institutional partnerships with biomedical labs and physics departments.
- Ethical review board approval for animal and human studies.
- Data transparency and publication in peer-reviewed journals.

Conclusion

Designing a robust and ethically sound experimental protocol is fundamental to transitioning Pyramid Energy Therapy from a theoretical framework to a scientifically validated treatment model. The experimental structure described herein serves as the foundation for this transformation.

Figures, diagrams, and charts detailing the setup of pyramid chambers, sensor placement, and energy field distribution will be included in the final version.

Chapter 11

XI. Ethical Considerations and Scientific Integrity in Pyramid Energy Therapy

a) *Introduction*

As pyramid energy therapy (PET) garners increasing attention as a potential complementary approach to cancer treatment, it becomes essential to address the ethical dimensions of its development, testing, and application. Given the vulnerable state of patients with cancer and the experimental nature of pyramid-based energy therapies, rigorous ethical standards must be upheld to ensure patient safety, dignity, and trust.

Figure 14

b) *Respect for Human Dignity*

Respecting human dignity is foundational in any therapeutic context. In PET, patients must not be treated as mere subjects or data points. Instead, they should be considered autonomous individuals with intrinsic value, deserving of empathy, transparency, and informed involvement in their treatment.

- Patient-centered approach: Practitioners must ensure that each individual's cultural, psychological, and spiritual needs are acknowledged.
- Avoiding objectification: Patients participating in experimental therapies must be shielded from any form of exploitation or reductionism.

c) *Scientific Rigor and Transparency*

To maintain legitimacy and foster trust in PET, researchers and practitioners must adhere to scientific principles:

- Evidence-based design: Therapies should be developed based on a solid foundation of empirical research, including peer-reviewed studies, reproducible experiments, and standardized methodologies.
- Transparent reporting: Results of clinical trials, whether favorable or not, must be made publicly accessible. Selective publication undermines scientific integrity.
- Peer review and replication: Theories and therapeutic claims should be evaluated by independent experts and subjected to replication before being accepted or promoted.

d) *Informed Consent and Patient Autonomy*

Patients must have the autonomy to choose or reject PET without coercion or misinformation.

- *Comprehensive information:* Before participation, patients must receive clear and understandable explanations of the therapy, including its experimental nature, potential benefits, and risks.
- *Voluntary participation:* Consent must be obtained freely, without undue pressure or manipulation, particularly from those in positions of authority or trust.
- *Right to withdraw:* Participants should retain the right to exit the therapy at any stage without facing repercussions.

e) *Ethical Challenges in Alternative Therapies*

PET exists within the broader category of alternative and complementary medicine, which poses unique ethical dilemmas:

- *False Hope Vs. Healing Potential:* It is unethical to promise or imply guaranteed cures. Any therapeutic claims must be presented with scientific caution and humility.
- *Misinformation and Pseudoscience:* Practitioners must distance themselves from unfounded claims or practices that could harm patients or erode credibility.
- *Regulatory Oversight:* There must be collaboration with health authorities and ethical review boards to ensure adherence to safety standards and scientific protocols.

f) *Safeguards against Exploitation*

Given the often desperate situations of patients with advanced illnesses, ethical safeguards are critical:

- *Affordable Access:* PET should not become a privilege only for the wealthy. If still under investigation, participation should be free or minimally charged.
- *Monitoring and Accountability:* Independent committees must oversee the implementation of PET, ensuring ethical conduct and immediate response to adverse events.
- *Education and Training:* Practitioners must undergo proper training in ethical standards, patient communication, and responsible research practices.

g) *Conclusion*

Ethical considerations and scientific integrity are not peripheral to the development of pyramid energy therapy-they are central. As this modality evolves, its credibility and potential depend heavily on transparent science, patient-centered care, and unwavering adherence to ethical principles. By embedding these values at every stage, PET can be explored responsibly as a possible tool in the broader landscape of cancer therapy.

Chapter 12

XII. Challenges and Limitations in the Implementation of Pyramid Energy Therapy

a) *Introduction to the Scope of Challenges*

As the concept of Pyramid Energy Therapy (PET) gains attention in the field of alternative medicine,

numerous challenges emerge that hinder its mainstream acceptance and application. These obstacles span across scientific, technical, cultural, and ethical domains, necessitating a holistic understanding of the barriers in order to facilitate responsible and evidence-based integration.

Figure 15

b) Scientific Skepticism and Lack of Consensus

One of the most prominent barriers is the lack of empirical consensus regarding the efficacy of PET. Mainstream science often views pyramid energy as pseudoscientific due to insufficient peer-reviewed data. The absence of repeatable, controlled experiments and a unified theory explaining how pyramid structures influence biological systems fuels skepticism among researchers and clinicians.

c) Technical Limitations in Pyramid Construction and Standardization

Constructing therapeutic pyramids with precise geometrical proportions, material consistency, and orientation to true north poses a significant challenge. Variability in construction methods can lead to inconsistent energy distribution, undermining the reproducibility and effectiveness of the therapy. Standardizing pyramid dimensions and materials is crucial for clinical validation.

d) Measurement and Quantification Difficulties

Measuring the bioenergetic fields or energetic resonance purportedly emitted by pyramid structures remains difficult with current scientific instruments. Without objective tools to quantify these energy interactions, PET lacks a measurable basis that would allow for systematic study, optimization, and clinical application.

e) Integration with Conventional Cancer Therapies

PET's integration with existing oncology protocols presents additional obstacles. Medical professionals often hesitate to combine conventional therapies with unverified alternatives due to concerns about interference, patient safety, and legal liability. Establishing a clear framework for complementary use, supported by clinical studies, is essential.

f) Cultural and Institutional Resistance

Despite rising interest in holistic and energy-based healing modalities, many institutions and cultures remain resistant to unconventional approaches. Medical curricula rarely include education on energy therapies, and regulatory bodies may not have frameworks to evaluate or approve such modalities. This institutional inertia slows research funding, clinical trials, and public acceptance.

g) Ethical and Legal Barriers

Ethical concerns regarding the exploitation of vulnerable patients, misrepresentation of scientific data, and lack of regulatory oversight pose serious challenges. Without clearly defined legal and ethical boundaries, PET could face backlash from both the public and medical communities. Developing professional guidelines and patient protections is necessary for legitimacy.

h) Conclusion: Overcoming the Barriers

While the challenges facing Pyramid Energy Therapy are substantial, they are not insurmountable. A multidisciplinary effort involving open-minded researchers, ethical practitioners, and patient advocacy groups is essential. By addressing the scientific, technical, cultural, and legal limitations, PET can be responsibly developed and potentially recognized as a viable complementary therapy in the battle against cancer.

Chapter 13

XIII. Future Research Directions and Innovation In Pyramid Energy Therapy

a) Introduction: The Need for Rigorous Scientific Exploration

As Pyramid Energy Therapy (PET) enters the scientific spotlight, there is a compelling need to establish structured, evidence-based research methodologies. Future progress depends on robust interdisciplinary collaborations that integrate physics, medicine, biology, and technology to uncover the mechanisms and applications of pyramid-based healing.

Figure 16

b) *Proposed Experimental Frameworks and Clinical Trials*

Establishing controlled, double-blind clinical studies is critical to assess the therapeutic impact of PET. Researchers should define clear metrics-such as tumor regression rates, patient-reported outcomes, and physiological markers-to validate effectiveness. Animal studies and in vitro cellular models can help uncover mechanisms before moving to human trials.

c) *Development of Precision Pyramid Technology*

Future innovation in PET will likely revolve around the design and fabrication of pyramids using nanomaterials, electromagnetic-sensitive substrates, and programmable configurations. 3D printing and smart materials may enable adaptive pyramids that self-calibrate according to patient-specific energetic needs.

d) *Biofield Mapping and Advanced Imaging Techniques*

New imaging modalities such as magnetic field tomography, thermographic sensors, and quantum resonance analysis could help visualize biofield fluctuations under PET. Mapping changes in cellular energy profiles during and after therapy sessions will provide insights into energetic interactions and healing responses.

e) *Synergistic Therapies: Combining Pyramid Energy with Other Modalities*

PET's efficacy may be enhanced when integrated with other non-invasive therapies such as sound healing, infrared therapy, and pulsed electromagnetic fields (PEMF). Exploring the synergistic effects of such combinations can open avenues for holistic, multimodal cancer treatment strategies.

f) *Artificial Intelligence in Pyramid Energy Optimization*

Artificial Intelligence (AI) and machine learning algorithms can analyze large datasets from PET sessions to optimize pyramid design, session duration, orientation, and environmental parameters. Predictive models may help tailor therapy plans to individual energetic signatures, improving outcomes and consistency.

g) *Institutional Collaborations and Funding Pathways*

Advancing PET research requires cross-institutional support, including academic partnerships, government grants, and private sector investment. Establishing dedicated research centers and publishing in reputable journals will increase visibility and credibility.

h) *Conclusion: A Roadmap for Transformative Discovery*

The future of Pyramid Energy Therapy holds significant promise if pursued with scientific integrity, technological innovation, and collaborative spirit. By laying down rigorous research pathways today, the next generation of scientists and clinicians can unlock the full therapeutic potential of pyramid energy in combating cancer and enhancing human health.

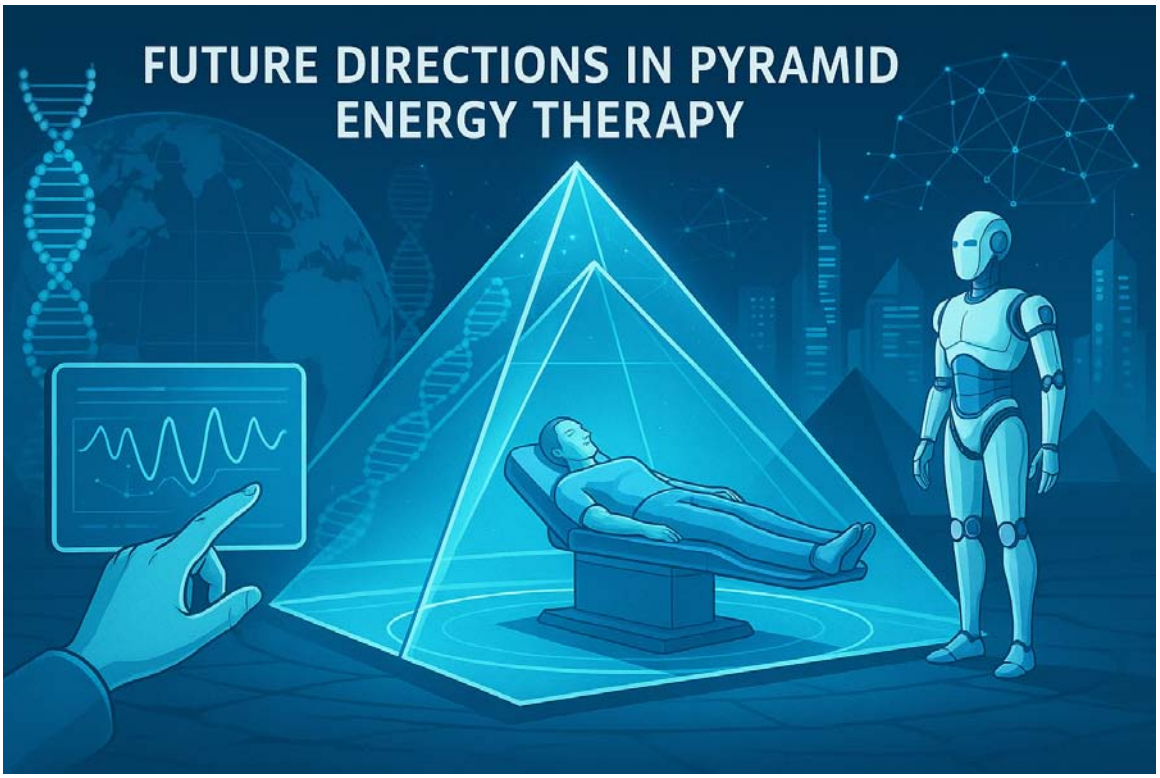

Figure 17

Chapter 14

XIV. Final Summary and Strategic Recommendations

1. Comprehensive Summary of Findings
   - This research has demonstrated the potential therapeutic role of pyramid-shaped structures in modulating energetic balances at the quantum level within biological tissues.
   - The pyramid energy framework provides a non-invasive, non-toxic complementary approach to addressing cellular energy imbalances, particularly in malignant cells.
2. Strategic Vision for Implementation
   - Establish standardized pyramid therapeutic chambers based on precise geometric specifications and electromagnetic alignment.
   - Develop protocols for patient positioning, exposure duration, and environmental control to maximize efficacy.
3. Policy and Clinical Integration
   - Advocate for the inclusion of pyramid energy modalities within integrative oncology frameworks, in alignment with guidelines by NCCIH, NCI, and ASCO.
   - Encourage clinical trials and observational studies to evaluate safety, efficacy, and quality-of-life outcomes.
4. Scientific Collaboration and Technological Advancements
   - Launch international collaborations to standardize research methodologies and share empirical data.
   - Develop advanced biophysical instrumentation for detecting and measuring bioenergetic field changes in response to pyramid therapy.
5. Concluding Message
   - A call to action for researchers, clinicians, and policymakers to explore ancient wisdom through
   - the lens of modern science.
   - Propose the foundation of an interdisciplinary Global Pyramid Research Institute to unify efforts and validate applications of pyramid energy in medical science.

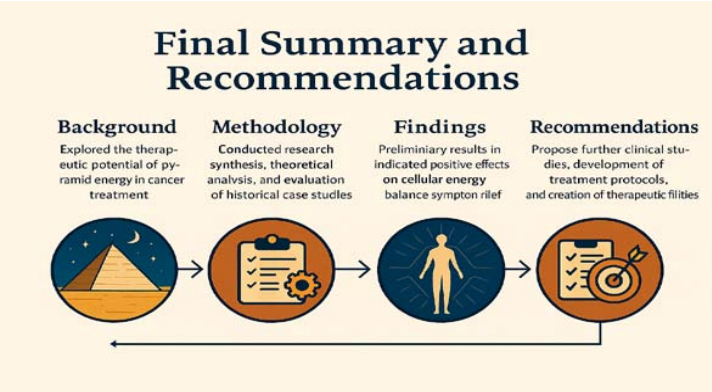

Figure 18

Chapter 15

xv. Feasibility Assessment and Future Challenges

a) Introduction

In the pursuit of integrating Pyramid Energy Therapy (PET) into an approved clinical framework, a comprehensive feasibility assessment becomes essential. This includes anticipating the potential challenges that may hinder the realization of this objective.

b) Scientific Feasibility Assessment

The formal adoption of pyramid energy as a recognized therapeutic path requires solid scientific support through laboratory and clinical experiments. The scientific feasibility rests upon the following pillars:

- A theoretical foundation rooted in atomic structure and the energetic nature of the cell.
- The ability to measure changes in the energetic balance of affected cells.
- Preliminary evidence suggesting that the pyramid field exerts measurable physical effects on biological structures.

c) Technical Challenges

- The difficulty in designing highly sensitive instruments capable of detecting minute energetic fluctuations within the cell.

d) Scientific and Academic Challenges

- Limited number of peer-reviewed studies published about pyramid energy.
- Conservative attitudes in traditional academic circles toward unconventional energy therapies.
- The necessity for collaboration with international universities and research centers to conduct randomized controlled trials (RCTs).

e) Ethical and Regulatory Challenges

- The need for a clear legal framework to govern the practice of this type of therapy and protect
- The requirement to subject pyramid chambers and treatment methodologies to reliable testing for safety assurance.
- Oversight by scientific research ethics committees to monitor the development of studies and document their results.

f) Opportunities for Funding and Institutional Support

- The possibility of obtaining support from innovation research centers and universities interested in complementary therapies.
- Collaboration with nonprofit medical organizations to fund pilot studies.
- The potential to patent the therapeutic pyramid chamber design and use it as a future funding source.

g) Conclusion

Feasibility assessment is inseparable from recognizing the challenges and addressing them through disciplined scientific methods. With a proactive approach, pyramid energy therapy may one day become an officially recognized option within the field of integrative medicine.

Chapter 16

xvi. Global Practices of Pyramid-Shaped Healing and Structural Bio-Energy

a) Introduction

While Pyramid Energy Therapy (PET) continues to mature within laboratory and pilot-clinical settings, a number of wellness centres and research initiatives around the world have already integrated pyramid-shaped structures into daily therapeutic routines. This chapter surveys those contemporary applications, evaluating their operational models, claimed benefits, and the current evidence base supporting their practices.

b) *Indonesia: The Pyramids of Chi, Ubud – An Acoustic Bio-Resonance Model*

Located in the rainforest terraces of Ubud, Bali, the Pyramids of Chi consists of two 14-m-tall canvas-on-steel pyramids precisely aligned to magnetic north. Daily 'Ancient Sound Healing' sessions employ gongs, didgeridoos, and Himalayan singing bowls to generate low-frequency acoustic fields that reverberate within the pyramid cavity. Clients report deep relaxation, improved sleep quality, and reductions in perceived stress. The centre's popularity demonstrates a viable tourism-health hybrid model that finances continued experimentation with acoustic bio-resonance inside pyramidal volumes.

Figure 19

c) *United States: Pyramid Village, Florida – Residential Wellness Infrastructure*

Pyramid Village in Fort Myers comprises 26 glass-and-aluminium chalets arranged around a geothermal lake. Conceived by Austrian engineers in the late 1990s, the resort markets the pyramid as a form that 'optimises subtle energies' for detoxification and musculoskeletal recovery. On-site programmes combine hydrotherapy, yoga, and light-therapy sessions within the chalets, attracting long-stay guests seeking integrative convalescence.

Figure 20

d) *Russian Federation: The Golod Pyramids – Large-Scale Public Experiments*

Engineer Aleksandr Golod constructed more than a dozen fibreglass pyramids up to 44 m high across Russia and Ukraine. Non-peer-reviewed field studies attributed to Golod claim enhanced immune response in volunteers, faster seed germination, and suppression of pathogenic bacteria-effects hypothesised to arise from spatial charge separation within the pyramid geometry. Although methodological transparency is limited, the scale of the installations offers a living laboratory for future controlled trials.

Figure 21

e) *Bosnia & Herzegovina: The Visoko 'Pyramids of the Sun' Complex – Geobiological Claims*

Guided tours through the Ravne underground tunnels near Visoko expose visitors to a reportedly high concentration of negative ions and low electromagnetic noise. Preliminary physiological monitoring suggests transient drops in heart-rate variability indices associated with stress. The site illustrates how heritage tourism can intersect with experimental geobiological wellness practices, though rigorous clinical data remain sparse.

Figure 22

f) *Emerging Clinical and Architectural Research*

Small animal studies indicate that housing under pyramid structures can mitigate neuroendocrine and oxidative stress markers, lending pre-clinical support for pyramid-mediated homeostasis. Parallel architectural proposals envision hospital wards built as nested pyramid shells to exploit natural ventilation, daylight, and alleged shape-induced bio-energetic benefits. Pilot projects are under development in India and Egypt.

Figure 23

g) *Comparative Analysis and Lessons for PET Development*

Across these diverse contexts, common operational themes emerge: (i) precise geometric construction aligned to true north, (ii) integration of complementary modalities (sound, light, hydro- or yoga-therapy), and (iii) a strong experiential narrative emphasising subtle-energy optimisation. For researchers, these implementations offer real-world testbeds to evaluate user safety, dosing parameters (duration, frequency), and scalable business models that could support future randomised, controlled investigations.

Figure 24

h) Conclusion

The existence of functioning pyramid-based wellness centres across four continents provides pragmatic evidence that PET concepts are already influencing health-seeking behaviour. Although scientific validation is incomplete, the operational data, client testimonies, and emerging bio-marker studies collectively justify expanded research into structural bio-energy. Systematic documentation of these global practices will strengthen the translational pipeline from experimental physics to integrative oncology.

Chapter 17

XVII. Ethical Considerations and Scientific Integrity

a) Introduction

As pyramid energy therapy advances toward clinical investigation and possible integration into healthcare systems, it is imperative to uphold the highest standards of ethics and scientific integrity. This chapter explores the moral obligations, research responsibilities, and regulatory expectations associated with studying and applying an alternative energy-based treatment for cancer.

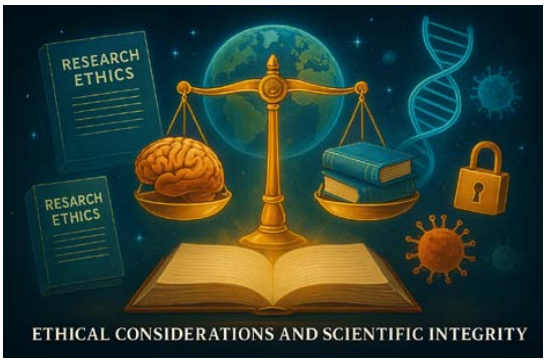

Figure 25

1. Informed Consent and Patient Autonomy
Patients have the right to understand the nature, purpose, and potential outcomes of any experimental therapy:
   - Full disclosure of pyramid therapy's experimental status.
   - Avoiding exaggerated claims or implied guarantees.
   - Ensuring patient decisions are voluntary, without coercion.
2. Avoiding False Hope and Medical Misrepresentation
Alternative therapies often attract patients with advanced disease or limited options. It is ethically vital to:
   - Present pyramid therapy as complementary, not curative or primary treatment.
   - Clearly state the current lack of large-scale clinical validation.
   - Encourage parallel use with evidence-based medicine.
3. Scientific Rigor in Research

Maintaining research integrity is essential to earn respect within the scientific and medical communities:
   - Apply standardized methodologies, including control groups and blinding when possible.
   - Publish results transparently, whether positive or negative.
   - Engage third-party validation and peer review.
4. Regulatory and Institutional Oversight
All clinical studies must comply with international and national regulations:
   - Secure approval from ethics committees and institutional review boards (IRBs).
   - Follow the Helsinki Declaration and Good Clinical Practice (GCP) guidelines.
   - Protect patient data privacy and adhere to biosafety standards.
5. Cultural Sensitivity and Respect
   - Energy-based therapies may be rooted in spiritual or traditional beliefs.
   - Respect cultural interpretations without misappropriating indigenous knowledge.
   - Avoid framing pyramid energy therapy in purely mystical or religious terms in scientific contexts.
6. Balancing Innovation with Responsibility
Scientific innovation should not override moral responsibility.
   - Carefully weigh potential benefits against unknown risks.
   - Ensure that exploratory studies are preceded by robust in-vitro and animal testing when applicable.
7. *Conclusion*

Ethical clarity is the foundation upon which pyramid energy therapy must be built if it is to gain legitimacy in the medical field. By fostering transparency, patient protection, rigorous research, and cultural sensitivity, this alternative modality can be responsibly explored as part of the broader search for holistic approaches to cancer treatment.

Chapter 18

XVIII. Experimental Design: using an egg as a Model for Cellular Response to Pyramid Energy

a) Introduction

This experiment aims to investigate the potential effects of pyramid-shaped structures on biological matter by using a chicken egg as a model for a living cell. The hypothesis is based on the concept that biological cells, composed of subatomic energy fields, may respond to the unique energy distribution within a pyramid.

b) Objective

To observe and analyze potential structural or energetic changes in a chicken egg after exposure to a pyramid-shaped healing chamber for a specified duration.

c) Materials and Equipment

- 1 raw chicken egg (uncooked, room temperature).
- Transparent pyramid model with exact geometric proportions (e.g., replica of the Great Pyramid).
- Timer or stopwatch.
- Thermometer (optional, to monitor environmental variables).
- Notebook or digital device for documenting observations.
- Camera for visual documentation.

d) Procedure

1. Place the raw chicken egg gently on a non-conductive support inside the pyramid, aligning it with the vertical axis.
2. Ensure that the environment is stable, with minimal external interference.
3. Leave the egg inside the pyramid for a defined duration (e.g., 24, 48, and 72 hours).
4. Take periodic photos and notes on visual appearance, consistency, smell, or any observable changes.
5. After exposure, compare the egg with a control egg (not placed in the pyramid) under the same environmental conditions.

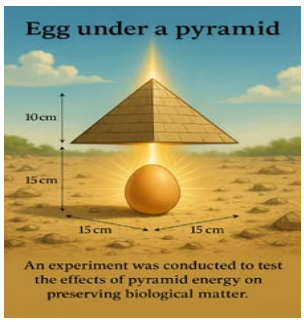

Figure 26

e) Data Collection and Observation

Carefully document any changes observed in the egg. Look for signs of dehydration, yolk stabilization, protein coagulation, or absence of odor typically associated with decay. Compare control vs experimental results.

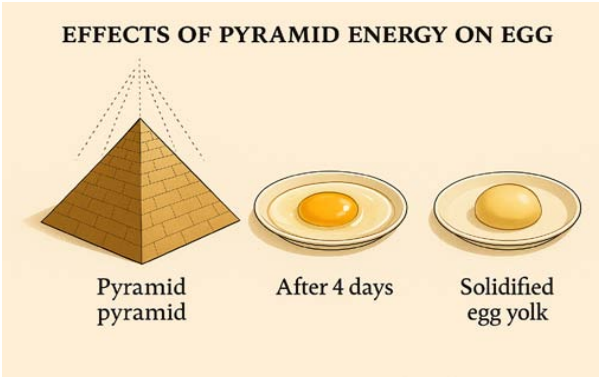

Figure 27

f) Expected Results

It is hypothesized that the pyramid's geometric energy field may help preserve the egg or trigger changes indicating subtle energetic effects, such as altered viscosity or improved structural integrity, consistent with previous pyramid energy studies.

g) Scientific Relevance

This experiment serves as a preliminary step to assess biological energy interaction with geometric fields. If results are promising, they could justify more advanced studies on energy-based cancer therapy models using actual cellular systems.

Figure 28

Chapter 19

XIX. Final Vision and Philosophical Reflections

a) Introduction

This final chapter offers a contemplative synthesis of the ideas, efforts, and aspirations woven

throughout this research. More than just a scientific hypothesis, pyramid energy therapy invites us to revisit ancient wisdom through the lens of modern science, urging humanity to rediscover balance, energy, and healing beyond conventional paradigms.

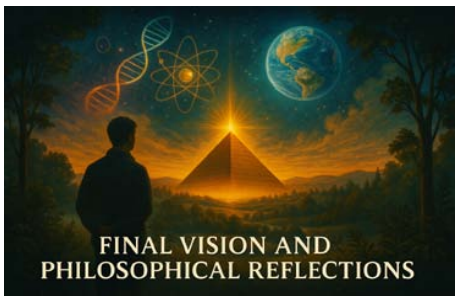

Figure 29

1. Revisiting the Journey From its theoretical foundation in quantum and energetic models of the cell, to the experimental frameworks and ethical considerations, this research has charted a visionary pathway. It proposes that life is not solely biochemical, but profoundly energetic. The pyramid-once a monument-is now a candidate for medical innovation.
2. The Pyramid as Symbol and Instrument The geometric perfection of the pyramid is more than architecture-it may embody harmonic resonance with Earth's magnetic field, cosmic alignment, and cellular organization. When repurposed as a healing structure, it becomes:
   - A sanctuary of energetic coherence
   - A space where form influences function
   - A bridge between ancient spiritual architecture and modern therapeutic environments
3. Philosophical Resonance

Pyramid energy therapy challenges us to expand our definition of healing. It suggests that:

- Healing is not just the removal of disease, but restoration of harmony.
- Energy fields may be as vital as chemistry.
- The human body responds not only to substances, but to form, frequency, and light.

4. Humanistic and Ethical Vision

This research upholds that every patient deserves dignity, choice, and hope. If pyramid energy can offer a gentle, supportive adjunct to healing, it must be explored with compassion, not skepticism; with open inquiry, not dismissal.

5. A Call to Science and Spirit

We invite scientists, physicians, engineers, and healers to collaborate. To unite empirical tools with intuitive insights. To embrace an inclusive paradigm where innovation meets humility.

Let the pyramid stand not only as a relic of the past-but as a beacon of a future where healing is multi-dimensional.

Closing Words

1. This work is not a conclusion-it is an invitation. An invitation to study, to challenge, to dream.
2. An invitation to bring ancient geometry into clinical reality.
3. An invitation to rethink healing as energy in balance.
   - Let the research continue.
   - Let the vision expand.
   - Let the healing begin.

XX. Conclusion: The Awakening of a New Healing Paradigm

As this research journey reaches its formal conclusion, it does not mark an end-but rather the ignition of a profound beginning. Pyramid Energy Therapy (PET), once considered a mystical relic of forgotten civilizations, now stands at the intersection of empirical science and visionary medicine. What began as a hypothesis rooted in geometry and energy has evolved into a blueprint for a new chapter in integrative oncology.

We have explored the possibilities that geometry may speak a language far deeper than structure-that it may, in fact, orchestrate harmony within the living body through subtle energetic codes. We have examined ancient echoes and modern resonance, theoretical models and experimental glimpses, in search of a truth that dares to transcend conventional boundaries.

If this research has shown anything, it is that healing is not confined to chemicals or machines-it may also be encoded in form, in frequency, in the silent intelligence of shape. The pyramid, in this vision, is not merely a monument of stone, but a whisper from the universe inviting us to look again at the fundamentals of life.

Let this work be an invitation, not a declaration. Let it spark questions more than answers, curiosity more than certainty. For in that space of inquiry-between what we know and what we dare to explore-lies the real medicine of the future.

The vision of PET is not one of replacement but of resonance. It seeks to live alongside modern medicine, not against it. To offer new hope where the old paths falter. To illuminate possibilities that have long been dismissed as speculative, yet are now emerging through the cracks of the known.

In the end, this is not just a scientific exploration. It is an awakening.

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Foundational Principle of the Research

- All matter, whether living or non-living, can be understood as a form of energy organized in specific patterns.
- At the most fundamental level, any substance can be deconstructed into molecules, atoms, and subatomic particles.
- Atoms consist of protons (positive charges) and electrons (negative charges), and these electric charges are essentially manifestations of energy.
- Thus, the fundamental building block of matter is a pair of energetic opposites-positive and negative energy states-organized into structured units we call atoms.
- The diversity of elements arises from the specific configurations of these energy units, giving rise to the periodic table.
- These elements combine to form compounds and materials that constitute the microscopic structure of all living cells.
- A living cell, therefore, can be described as a highly organized and balanced network of energy units in dynamic equilibrium.
- When this energy balance is disturbed, as in the case of cancer cells, the cellular function becomes erratic and destructive.
- The hypothesis of this research proposes that restoring energetic equilibrium to a diseased cell-especially a cancer cell-could return it to normal function.
- This approach aims to heal the cell without causing the collateral damage associated with conventional therapies like chemotherapy or radiation.
- It opens the door to exploring new, non-invasive, energy-based methods for treating cancer at its foundational energetic level.

Figure 30

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Self-Care for Arteriovenous Fistula and the Prevalence of Depression, Anxiety, Stress and Resilience

By Soraia Geraldo Rozza, Bianca Nantes Nunes, Daniel de Macedo Rocha & Gilmar Jorge de Oliveira Júnior

Universidade Federal de Santa Catarina

Resumo- A doença renal crônica afeta mais de 10% da população mundial, constituindo uma preocupação global de saúde pública. Pacientes com doença renal crônica frequentemente necessitam de hemodiálise e fazem uso da fístula arteriovenosa, que demanda cuidados específicos. Esses pacientes também podem enfrentar condições como depressão, ansiedade e estresse, com a resiliência desempenhando um papel fundamental no enfrentamento dessas adversidades.

O Objetivo: deste estudo é investigar a associação entre resiliência, sintomas de depressão, ansiedade e estresse e os comportamentos de autocuidado relacionados à fístula arteriovenosa em pacientes hemodialíticos.

Método: Trata-se de um estudo observacional, transversal, de caráter descritivo-analítico, conduzido em quatro serviços de Nefrologia na Região Centro-Oeste do Brasil. Foram aplicadas a "Escala de Resiliência", a "Escala de Depressão, Ansiedade e Estresse" e a "Escala de Avaliação de Comportamentos de Autocuidado com a Fístula Arteriovenosa em Hemodiálise".

Palavras-Chave: doença renal crônica, hemodiálise, autocuidado, ansiedade, depressão, estresse, resiliência.

GJMR-K Classification: NLMC: WM 171

Strictly as per the compliance and regulations of:

Self-Care for Arteriovenous Fistula and the Prevalence of Depression, Anxiety, Stress and Resilience

O Autocuidado Com A Fístula Arteriovenosa E A Prevalência Da Depressão, Ansiedade, Estresse E Resiliência: Um Estudo Epidemiológico E Observacional

Soraia Geraldo Rozza [α], Bianca Nantes Nunes [σ], Daniel de Macedo Rocha [ρ] & Gilmar Jorge de Oliveira Júnior [ω]

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"O Presente Trabalho Foi Realizado Com Apoio Da Coordenação De Aperfeiçoamento De Pessoal De Nível Superior - Brasil (CAPES) - Código De Financiamento 001"
This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) - Finance Code 001.

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Resultados: Os resultados indicaram que não houve associação significativa entre os comportamentos de autocuidado e as variáveis estudadas. Conclusão: Apesar da ausência de associação entre os fatores analisados, o estudo evidenciou que a ansiedade é um sintoma predominante entre os pacientes hemodialíticos. Além disso, destacou a importância do autocuidado com a fístula como componente essencial para o cuidado integral em saúde e a saúde mental desses pacientes.

Author α: Professora do Mestrado em Enfermagem do INISA/UFMS. Doutora em Enfermagem pela Universidade Federal de Santa Catarina (UFSC).
Author σ: Graduada em Enfermagem pela Universidade Federal de Mato Grosso do Sul (UFMS), Câmpus de Coxim. Mestre em Enfermagem pelo INISA/UFMS, sob a orientação da Professora Dra. Soraia Geraldo Rozza.Aluna do Doutorado no Programa de Saúde e Desenvolvimento na Região Centro-Oeste no PPGSD/FAMED/UFMS.
Author ρ: Doutor em Enfermagem. Professor do Curso de Enfermagem daUniversidade Federal de Mato Grosso do Sul (UFMS), Câmpus de Coxim.
Author ω: Professor de Estatística na Universidade Federal de Mato Grosso (UFMT).

Palavras-Chave: doença renal crônica, hemodiálise, autocuidado, ansiedade, depressão, estresse, resiliência.

I. Introdução

A doença renal crônica (DRC) está inserida no grupo das doenças relacionadas à civilização moderna, assim como as doenças cardiovas culares comuns, a hipertensão e a diabetes. Segundo Canaud*et al*. (2024) e Monárrez-Espino*et al*. (2021), a preocupação com essa doença se amplia quando se nota o aumento dos casos em que ela sofre combinação com outros fatores de risco, como o envelhecimento e as comorbidades. A DRC é irreversível e compromete progressivamente a saúde e a qualidade de vida dos pacientes (QV).

De acordo com Ozen *et al*. (2025) e Borg *et al*. (2023), a prevalência da DRC é uma preocupação global de saúde pública, pois ela está aumentando rapidamente em todo o mundo. Nesse sentido, Ferreira *et al*. (2024) pontuam que a DRC acomete mais de 10% da população mundial, com aproximadamente 840 milhões de pessoas atingidas. Observadas as proporções continentais, a prevalência da DRC é estimada entre sete por cento na Ásia e 12% por cento na Europa, e de 10,1% a 15,8% na África, conforme García-Martínez *et al*. (2021) e Ulasi*et al*. (2022).

Borg*et al*. (2023) preveem que até 2040 a DRC se tornará a quinta condição crônica mais prevalente, ao passo que Ledo *et al*. (2024) estima que nesse mesmo ano ela se tornará a terceira causa mais comum de mortalidade, ampliando o cenário já preocupante dos custos de tratamento.

Na perspectiva de Martins e Moura (2023, p. 2), a DRC pode ser definida como uma "lesão renal que origina uma perda progressiva e irreversível da função renal, glomerular, tubular e endócrina, evoluindo ao

manter a homeostasia interna. Essa severa disfunção requer do paciente a adesão a um tratamento de substituição da função renal sendo a hemodiálise o tratamento de eleição e o mais comumente adotado.

Há três tipos de AV para a realização da HD e os quais possuem uma diferente vida útil, a saber, o cateter venoso central, o enxerto arteriovenoso e a fístula arteriovenosa (FAV). Existem AV permanentes e AV temporários, sendo a FAV o AV permanente de eleição, sendo o mais seguro e o mais duradouro para a realização da HD, conforme Martins e Moura (2023) e Qian *et al*. (2020).

A FAV é uma anastomose autógena entre uma artéria e uma veia. Nesse sentido, Correia *et al*. (2021) explicam que depois da criação da FAV, um fluxo contínuo da artéria para a veia principia diversas mudanças, alterando a estrutura da parede, gerando uma tensão de cisalhamento, e aumentando intensamente o fluxo sanguíneo durante as primeiras 24 horas.

As etapas pelas quais ocorre a inserção da FAV são três, e um descuido em qualquer uma delas pode prejudicar todo o processo. Primeiro, um cirurgião deve colocar a FAV; em seguida, precisa haver a maturação da FAV levando ao seu uso bem-sucedido para diálise. Por fim, deve-se proceder à manutenção da patência da FAV primária após seu uso com sucesso.

Apesar de ser a indicação mais durável e segura no tratamento hemodialítico, a FAV requer muita atenção do paciente que dela faz uso, denotam Doroughe*t al*. (2021) e Costa Pessoa *et al*. (2020). Lira *et al*. (2021) afirmam que a disfunção desse acesso é uma das causas mais importantes de morbidade e mortalidade em pacientes em terapia hemodialítica. Essa disfunção pode ser responsável por até um terço das hospitalizações, o que implica consideráveis custos de saúde para esses indivíduos.

Ao requerer cuidados da FAV por parte do doente, a preocupação incide principalmente ao nível da prevenção da infecção e da trombose do AV. Dessa forma, os pacientes são orientados a adotar atitudes práticas de autocuidado, como não permitir coletas de sangue no braço que está com a FAV, proteger esse braço de pancadas e choques e avisar o enfermeiro caso perceba o aparecimento de feridas na mão do braço da fístula, conforme pontuam Martins e Moura (2023). Para essas estudiosas, diante da percepção de que a FAV é o melhor acesso para hemodiálise, é importante que os próprios pacientes adotem ações de autocuidado para manter a funcionalidade deste instrumento a fim de não comprometer o tratamento, mas o apoio do enfermeiro também pode fazer muita diferença nesse processo.

Bulbul *et al*. (2023) e Sousa *et al*. (2018) observam que na literatura há escassez de estudos sobre os perfis de comportamentos de autocuidado relacionados à FAV. Preocupados com essas questões, em 2015 pesquisadores portugueses Sousa *et al*. elaboraram a "Escala de Avaliação de Comportamentos de Autocuidado com Fístula Arteriovenosa em Hemodiálise". Em 2021, esses estudiosos interagiram com investigadores do Brasil para validar a versão brasileira da referida escala (Lira *et al*., 2021). Nessa validação, apenas algumas palavras foram modificadas por serem mais utilizadas no português brasileiro. Esse acesso mais recente será utilizado nesta pesquisa, conforme será detalhado no método.

Os estudos de Donahue *et al*. (2021) delineiam que as doenças crônicas, em especial a DRC, costumam trazer consigo a depressão, a ansiedade e o estresse. Sobre a depressão nos pacientes com DRC, observa-se que essa patologia é um dos transtornos psiquiátricos mais comuns. A prevalência de depressão é muito maior em pacientes em HD em comparação a outros indivíduos da população normal.

Como em outras condições de doenças crônicas e na população em geral, existem evidências de que a depressão em pacientes em HD está associada à mortalidade. Nos pacientes hemodialíticos a depressão é um problema comum. Se subdiagnosticado, pode tornar-se um fator de risco independente para o aumento da morbidade e mortalidade desses pacientes, ou resultar na desistência do tratamento, conforme evidenciam Bansal *et al*. (2023), Donahue *et al*. (2021) e Khan *et al*. (2019).

Nas pesquisas de Hagemann *et al*. (2019, p. 74-75), as condições clínicas e a própria rotina impostas pela HD são consideradas "fontes de estresse" que impõem extensas modificações na vida do paciente, "o que pode levar a umimpacto negativo sobre a QV relacionada à saúde, incrementando o estresse cotidiano e favorecendo a emergência de depressão", modificando "a percepção e a avaliação que o indivíduo faz de sua vida e de sua doença".

Acreditando que o enfrentamento das doenças pode ser viabilizado pela resiliência, esse termo é definido por Connor e Davidson (2003) e Connor e Zhang (2006) como sendo uma ferramenta imprescindível no tratamento da ansiedade, da depressão e do estresse que atingem os pacientes portadores de doenças como as crônicas.

Na literatura sobre os pacientes hemodialíticos não foi encontrada nenhuma pesquisa que tenha realizado associações entre resiliência, depressão, estresse e ansiedade e o autocuidado com a FAV. Há investigações que mensuram duas dessas variáveis com o autocuidado e nem sempre as escalas utilizadas são as mesmas que fizemos uso nesse estudo.

Alguns estudiosos também se ativeram a essa questão, optando por focar seus estudos sobre a presença da depressão nos pacientes hemodialíticos. Sharif *et al*. (2022) constataram que, apesar de existirem muitos relatos sobre os fatores de fundo sobre os sintomas depressivos em pessoas submetidas à HD,

mais informações são necessárias para esclarecer e confirmar os resultados em diferentes populações. Por isso, eles pontuaram que ainda é preciso investigar mais profundamente se esses fatores podem prever sintomas depressivos em pacientes submetidos à HD.

Para tanto, o objetivo deste estudo é verificar a associação de resiliência e sintomas de depressão, ansiedade e estresse com o comportamento de autocuidado com a FAV entre pessoas hemodialíticas.

II. Método

Trata-se de um estudo observacional, transversal, descritivo-analítico, de abordagem quantitativa. O método está em consonância com a modalidade de estudo STROBE, cujas diretrizes do *checklist* foram observadas.

O estudo foi desenvolvido em quatro serviços de Nefrologia na Região Centro Oeste do Brasil. Os critérios de inclusão foram: participantes com idade igual ou maior de 18 anos, com FAV e realizando tratamento hemodialítico há pelo menos seis meses depois da inserção da FAV. Nesses critérios também se incluíram os pacientes com boas condições cognitivas para responder aos questionários, para isso foi feito um contato prévio com a enfermeira responsável pelo setor a fim de se obter a relação dos participantes aptos nesse quesito. Já os critérios de exclusão foram estes: participantes com cateter venoso central, participantes com acesso vascular duplo (cateter venoso central e FAV) e internados no momento da coleta de dados.

Neste estudo não houve necessidade de definir técnicas de amostragem uma vez que foram definidos critérios de inclusão e após a sua aplicação foram todos incluídos no estudo. A amostra inicial era de 212 participantes,após a aplicação destes critérios obtivemos a exclusão de 100 pacientes. As razões que justificaram a exclusão foram: 78 possuíam cateter venoso central, nove recusaram-se a participar, um paciente estava internado, três eram menores de 18 anos e nove apresentavam limitação cognitiva.

A coleta dos dados iniciou-se em maio de 2024 e foi finalizada em julho desse mesmo ano. Foi aplicado um questionário sociodemográfico e clínico, assim como estas três escalas: a) Autocuidado com a FAV; b) Resiliência e c) Depressão, Ansiedade e Estresse.

O instrumento de coleta de dados empregado no estudo foi o questionário de caracterização sociodemográfica e clínica. Essa ferramenta mensura: a) a caracterização das variáveis sociodemográficas do doente renal crônico em programa de HD, como sexo, idade, estado civil, religião, situação profissional, nível de rendimentos; b) a caracterização das variáveis clínicas do doente renal crônico em programa de HD, como tempo de realização de HD, presença ou ausência de complicações durante a sessão de HD.

Nesta pesquisa será empregada a Escala de Resiliência proposta e validada por Connor e Davidson (2003), sendo trabalhada com a categorização. A proposição desse instrumento demonstra que, "ao concentrar-se nos pontos fortes e nos atributos positivos, um indivíduo tende a envolver-se em atividades mais adaptativas e os seus problemas tendem a diminuir" (2003, p. 81). Por isso, entende-se que a confiabilidade desse instrumento ficou bem delineada já que foi elaborado possuindo propriedades psicométricas sólidas, o que demonstra que ele pode ter utilidade potencial tanto na prática clínica quanto na pesquisa.

A escala de depressão é conhecida como Depressão, Ansiedade e Estresse (DASS - Depression, Anxietyand Stress Scale). Foram analisados os dados referentes a esses três constructos. A DASS foi desenvolvida como um instrumento para avaliar sintomas de depressão, ansiedade e estresse. É constituído por 42 questões de avaliação em 3 subescalas com 14 itens cada. Nessa investigação foi utilizada a versão proposta e validada por Vignola e Tucci (DASS-21).

Também foi aplicada a "Escala de Avaliação dos Comportamentos de Autocuidado com FAV em Hemodiálise" (Lira *et al*., 2021). A referida escala é composta por 16 itens distribuídos em duas subescalas: autocuidado na prevenção de complicações (PC) (10 itens) e autocuidado na gestão de sinais e sintomas (GSS) (seis itens). Cada item é pontuado de acordo com uma escala Likert de cinco pontos que varia de um (Nunca realizar o autocuidado) a cinco (Sempre realizar o autocuidado), de modo que a pontuação global deve variar entre 16 e 80 pontos. Calculando-se a razão entre o escore final e o máximo, encontra-se um valor percentual que representa a frequência de comportamentos de autocuidado do paciente com FAV, de maneira que, pontuações mais altas indicam maior frequência de comportamento de autocuidado com a FAV.

Até o presente momento, não foi encontrada nenhuma investigação que tenha agregado a aplicação dessas três escalas junto a pacientes hemodialíticos que fazem uso de FAV.

A pesquisa possui apreciação ética pelo Comitê de Ética em Pesquisa com Seres Humanos da UFMS sob o parecer nº 6.721.932. Os procedimentos de coleta de dados foram realizados após o CEP e assinatura do termo de consentimento Livre Esclarecido pelos participantes do estudo (TCLE). A coleta de dados foi registrada no *Google Forms* portando um celular, a entrevistadora indagou aos participantes os dados pertinentes ao questionário socioeconômico e as perguntas das três escalas. As aplicações dos instrumentos começaram uma hora após o paciente ter iniciado o tratamento na máquina e nunca aconteciam

antes dos 30 minutos finais da diálise deste. O tempo das entrevistas foi de 20 minutos.

Com os dados contidos na planilha gerada pelo *Google Forms*, esta foi importada. Foi feita a codificação e a categorização dos dados conforme necessidade inerente aos objetivos do estudo e frequências observadas. Posteriormente, eles foram migrados para o software Stata versão 14.0 onde foram realizadas as análises estatísticas.

A caracterização do público-alvo segundo as variáveis dependentes e independentes foi efetivada por meio de análise estatística descritiva, por meio da qual foram calculadas as medidas de tendência central e de dispersão/variabilidade para as variáveis quantitativas, já as variáveis qualitativas (categóricas) foram resumidas por meio de frequências absolutas e relativas. Na sequência foi aplicada o teste de normalidade (Kolmogorov Smirnov ou Shapiro-Wilk, dependendo do tamanho amostral final do estudo) nas variáveis de estudo, com o intuito de definir quais técnicas estatísticas serão utilizadas. No caso, os testes de normalidade devem ser aplicados aos dados de variáveis quantitativas, distribuídos ou não por categorias de variáveis qualitativas.

Posterior à análise descritiva, foi empregada análise bivariada, considerando a variável dependente como quantitativa, representada pelas frequências de comportamento de autocuidado com a FAV, de forma separada por subescala: frequência de autocuidado para prevenção de complicações e frequência de autocuidado para manejo de sinais e sintomas.

Foram realizadas análises de correlação de Pearson ou de Spearman, testes de comparação de médias ou medianas, teste de qui-quadrado, a fim de verificar fatores potencialmente associados ao comportamento de autocuidado com a FAV e também, identificar possíveis fatores interferentes na relação entre as variáveis independentes e a variável dependente.

Por fim, foram consideradas variáveis elegíveis para a análise múltipla aquelas para as quais se observar p-valor < 0,20 na análise bivariada. A intenção inicial foi a de aplicar a técnica de regressão linear, uma vez atendidos os pressupostos teóricos para a referida técnica, foram analisados os coeficientes de regressão como estimativas da relação estatística observada, os p-valores e os Intervalos de Confiança (95%) a fim de identificar os fatores associados, destacando-se aquelas variáveis em que se observar p-valor menor ou igual a 0,05. Essa opção se deveu ao fato de que a referida análise foi realizada em outro estudo, em que foi empregado o mesmo instrumento para mensurar a frequência do comportamento de autocuidado com a FAV (Sousa *et al*., 2017).

III. Resultados

Este estudo analisou dados de 112 pessoas com FAV em hemodiálise. Apesar do equilíbrio entre os sexos na composição amostral, observou-se que a maioria dos participantes eram procedentes da capital do estado 57(50,89%), apresentavam elevada taxa de alfabetização, tinham renda igual ou inferior a dois salários-mínimos 87(77,68%) e estavam sem trabalho remunerado. Quanto ao tempo de tratamento em hemodiálise, foi majoritariamente superior a 24 meses.

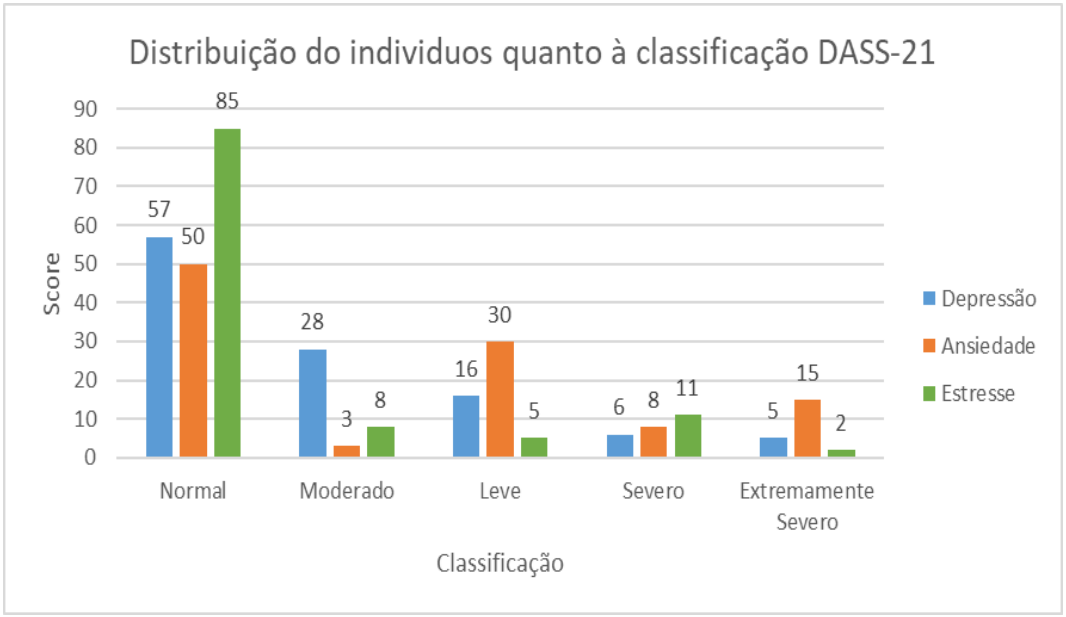
A tabela 1 apresenta os indicadores gerais de autocuidado na amostra investigada, assim como os escores para ansiedade, depressão, estresse e resiliência. Nesta dimensão, as estimativas globais apresentaram mediana de 33,59 e demonstraram limitações importantes na prevenção de complicações associadas à fístula e na gestão de sinais e sintomas durante o tratamento de hemodiálise. Embora a ansiedade tenha compreendido a alteração psiquiátrica prevalente em pessoas com FAV (52,83%), o estresse representou a condição com variável com maior estimativa média (11,11), demonstrando níveis de maior gravidade na amostra. Na ansiedade o escore médio para gravidade foi de 9,64 e na depressão de 9,62. O escore global de resiliência foi de 72,90.

Tabela 1: Indicadores De Autocuidado, Depressão, Ansiedade, Estresse E Resiliência De Pacientes Com FAV. Campo Grande, MS, Brasil. 2024

Desfecho	Média	Mediana	Mínimo	Máximo	IC (95%)	
					Inferior	Superior
Autocuidado	34,42	33,59	7,81	78,12	31,78	37,06
Depressão	9,62	8	0	28	8,14	11,11
Ansiedade	9,64	8	0	36	8,03	11,26
Estresse	11,11	10	0	36	9,39	12,82
Resiliência	72,90	74	35	100	70,62	75,18

Legenda: IC – Intervalo de Confiança

O rastreamento positivo para ansiedade, depressão e estresse, mesurado pelo DASS-21, foi classificado de acordo com a gravidade clínica (Gráfico 1). Quando presente, ansiedade prevaleceu em nível leve (30), a depressão em nível moderado (28) e o estresse em nível severo (11).



Fonte: Dados da pesquisa, 2024

Gráfico 1: Distribuição Dos Níveis De Gravidade Da Ansiedade, Estresse E Depressão Em Pessoas Com FAV. Campo Grande, MS, Brasil. 2024

A tabela 2 apresenta os resultados de associação entre as proporções de ansiedade, depressão, estresse e resiliência com os comportamentos de autocuidado apresentados pela amostra estudada. Nesta dimensão, não foram evidenciadas associações significativas entre os desfechos avaliados. Apesar disso, os indicadores de resiliência (55,10%), ansiedade (52,73%), estresse (52,83%) e depressão (54,55%) foram maiores em pessoas com maior capacidade para o autocuidado.

Tabela 2: Associação Entre Os Escores Dos Formulários DASS E De Resiliência Com O Autocuidado Da FAV. Campo Grande, MS, Brasil, 2024

Variável		Autocuidado FAV		Valor de p*
		Menor que a mediana (%)	Maior ou igual a mediana (%)	
Resiliência	Sim	22 (44,90%)	27 (55,10%)	0,341
	Não	34 (53,97%)	29 (46,03%)	
Depressão	Sim	25 (45,45%)	30 (54,55%)	0,345
	Não	31 (54,39%)	26 (45,61%)	
Ansiedade	Sim	26 (47,27%)	29 (52,73%)	0,571
	Não	30 (52,63%)	27 (47,37%)	
Estresse	Sim	25 (47,17%)	28 (52,83%)	0,570
	Não	31 (52,54%)	28 (47,46%)	

*Legenda: * Teste qui-quadrado*

Os resultados de associação entre os escores médios de ansiedade, depressão, estresse e resiliência com os comportamentos de autocuidado com a FAV está apresentado na Tabela 3. Na mesma perspectiva, não foram verificadas associações significativas. Ainda, esses resultados comprovam que os maiores indicadores médios de ansiedade (10, 32), depressão (10,25) e estresse (11,89) foram reportados por pessoas com índices mais elevados de autocuidado. Nesse mesmo grupo a pontuação média de resiliência foi de 70,53.

Tabela 3: Análise Dos Grupos Através De Teste Não-Paramétrico Mann-Whitney Para Verificar Diferença Entre Medianas Dos Grupos. Campo Grande, MS, Brasil, 2024

Variável	Autocuidado FAV		Valor de p*
	Menor que a mediana (n=56)	Maior ou igual a mediana (n=56)	
	Média [IC 95%]	Média [IC 95%]	
Resiliência	75,26 [72,10 ; 78,43]	70,53 [67,28 ; 73,78]	0,0626
Depressão	9 [6,89 ; 11,10]	10,25 [8,10 ; 12,39]	0,3980
Ansiedade	8,96 [6,78 ; 11,14]	10,32 [7,88 ; 12,76]	0,4927
Estresse	10,32 [7,92 ; 12,72]	11,89 [9,38 ; 14,41]	0,4117

IV. Discussão

Na análise de associação com os escores dos formulários de Resiliência e o DASS, em relação à escala de autocuidado (FAV Geral) (tabela 2), nenhum deles demonstrou haver associação estatisticamente visível. Então, tanto pelo teste qui-quadrado (tabela 1) quanto pelo teste Mann-Whitney (tabela 3), as variáveis Resiliência, Depressão, Ansiedade e Estresse, não são interessantes para o estudo, pois não apresentaram nenhuma associação com a variável resposta. Ou seja, a tabela 3 traz uma análise parecida com a análise da tabela 1, porém com uma abordagem diferente. O resultado foi o mesmo nas duas análises: não existe associação com o autocuidado.

O cálculo da prevalência feito a partir das tabelas permite perceber que a ansiedade compreendeu o traço de saúde mental mais comum em pessoas com FAV em tratamento hemodialítico, acometendo 52,83% dos participantes. A prevalência da depressão foi de 49,10%. Esses resultados diferem da literatura vigente para a qual a depressão é a alteração mais observada nos pacientes hemodialíticas, conforme observado nas buscas em plataformas científicas.

Nesse contexto, Chiou *et al*. (2023) realizaram uma investigação em cinco centros de hemodiálise de Taiwan, restringindo a pesquisa aos pacientes com mais de 40 anos de idade. Dos 179 participantes selecionados, 145 faziam uso da utilizando a versão chinesa da Escala de Depressão do Centro de Estudos Epidemiológicos (Escala CES-D). Essa pesquisa constatou que 60,3% dos participantes apresentaram depressão, confirmando os posicionamentos vigentes na literatura para a qual a proporção de sintomas depressivos é elevada nos pacientes em HD.

Os dados levantados também revelaram que o estado civil, o número de comorbidades, o comportamento de exercícios e o apoio social podem prever significativamente os sintomas depressivos; a variância explicativa total foi de 31,3%. Em sua conclusão, Chiou *et al*. também afirmam que os profissionais de saúde devem identificar os pacientes hemodialíticos com alto risco de sintomas depressivos a fim de conduzir-lhes para suporte em saúde mental.

Um estudo transversal e correlacional desenvolvido por Hae Ok Jeon*et al*. (2020) na Coreia do Sul com 71 pacientes constatou que 32,4% dos participantes estavam deprimidos. Os sintomas depressivos foram avaliados pela Escala de Depressão do Centro de Estudos Epidemiológicos (CES-D) e a fadiga pela Escala de Fadiga de Chalder.

Na Índia, Shanmukham*et al*. (2022) constataram que o problema psicológico mais prevalente foi identificado como depressão, com 41% dos pacientes apresentando resultado positivo para depressão clínica limítrofe.

Num estudo prospectivo de acompanhamento multicêntrico realizado na Malásia, a depressão foi prevalente. Fazendo uso da "Escala Hospitalar de Ansiedade e Depressão" (HADS), Khan *et al*. (2019) realizaram uma investigação na qual 220 indivíduos se mostraram pacientes elegíveis. Nesta investigação, 157 (71,3%) pacientes sofreram de depressão no início do estudo, 169 (78,2%) na 2ª avaliação e 181 (84,9%) na visita final, respectivamente. É interessante observar que a Escala HADS é composta por dois domínios: ansiedade (sete itens) e depressão (sete itens), porém no referido estudo não houve mensuração estatística da ansiedade. Essa observação principia nossa constatação de que há poucos estudos que mencionam a ansiedade.

Em nossa pesquisa, a depressão é percebida nos resultados percentuais elevados presenciados na aplicação da Escala DASS para os seguintes itens: "Não consegui vivenciar nenhum sentimento positivo", "Achei difícil ter iniciativa para fazer as coisas", "Senti que não tinha nada a desejar", "Senti-me depressivo (a) e sem ânimo", "Não consegui me entusiasmar com nada", "Senti que não tinha valor como pessoa" e "Senti que a vida não tinha sentido".

Na literatura são escassas as pesquisas sobre a ansiedade no contexto hemodialítico. Em Belo Horizonte, no Brasil, Brito *et al*. (2019) realizaram um estudo transversal, com 205 pacientes. A depressão foi mensurada em 41,7% ao passo que a ansiedade foi medida em 32,3%. Os níveis de depressão e ansiedade dos pacientes foram avaliados usando o Inventário de Beck.

Outra pesquisa que investiga a ansiedade juntamente com a depressão foi realizada em 2025 no Reino Unido. Os 458 participantes preencheram questionários de triagem para depressão e ansiedade, juntamente com perguntas sobre histórico de saúde mental, autoeficácia, tratamento e suporte. O estudo incluiu adultos (18 anos ou mais) vivendo com DRC. Sintomas moderados a graves de depressão e ansiedade foram 37,7% e 26,5%, respectivamente. Mais de 50% relataram histórico de depressão diagnosticada. Os sintomas de ansiedade e depressão foram medidos usando o questionário Generalised Anxiety-7 (GAD-7) e a versão de oito itens do Physical Health Questionnaire (PHQ-8). Essa investigação foi conduzida por Chilcot*et al*. (2025).

García-Martínez *et al*. (2021) elaboraram uma pesquisa que correlaciona as variáveis *estresse* e *resiliência*. Esses estudiosos espanhóis usaram a "Escala de Resiliência de Connor-Davidson (CD-RISC)", ao lado da "Escala de Estresse Percebido" e da "Escala da Qualidade de Vida da Doença Renal". A resiliência foi encontrada como o principal preditor de estresse percebido entre pacientes submetidos à HD por mais de seis meses.

Em relação à pesquisa mencionada acima, nas tabelas do nosso estudo, ao se considerar os escores de ansiedade, estresse e depressão em pessoas com FAV em hemodiálise, temos a constatação de que, quando presente, a gravidade prevalente foi leve para ansiedade, moderada para depressão e severa para o estresse percebido.

No momento das nossas entrevistas, ao aplicar as escalas DASS e CD-RISC e realizar uma autorreflexão automática sobre a natureza das perguntas, foi possível inferir que *em si mesmas*as variáveis *estressee resiliência* estão intrinsecamente interligadas, não sendo possível dissociá-las. Num importante estudo realizado na China em 2024, Tian *et al*. corroboram essa percepção ao lembrarem que já em sua definição a resiliência abarca e pressupõe o estresse. Por isso, no momento de realizar as entrevistas tivemos a certeza de que a aplicação das escalas DASS e CD-RISC foram escolhas acertadas. Isso justifica o fato de os pacientes não sentirem um estranhamento ou desconforto quando passávamos das perguntas da escala DASS para as da escala CD-RISC, tornando agradáveis as visitas hospitalares.

No estudo que realizamos, a resiliência foi mensurada com a média de 72,90% e a mediana em 74%. De certa forma, antes mesmo da divulgação estatística, esses resultados percentuais elevados já poderiam ser esperados, pois, no momento das entrevistas, diante das perguntas da Escala CD-RISC, os pacientes respondiam com entusiasmo, rememorando a resiliência predominante na sua maneira de enfrentamento às adversidades trazidas pela DRC.

Numa pesquisa empreendida no Irã, Saedi*et al*. (2024) utilizaram a "Escala de Resiliência de Connor-Davidson (CD-RISC)", o "Questionário de Adesão ao Tratamento (ATQ)", o "Questionário de Bem-Estar Psicológico Reef". A maioria dos participantes apresentava FAV. Juntamente com as variáveis *saúde espiritual* e *bem-estar psicológico*, a *resiliência* é um fator que afeta muito positivamente no tratamento hemodialítico, principalmente no que se refere ao aumento da adesão ao tratamento em pacientes submetidos à HD.

No México, González-Flores *et al*. (2021) conduziram um estudo que visava mensurar a resiliência como um fator de proteção contra depressão e ansiedade em pacientes mexicanos em diálise. A depressão e a ansiedade foram avaliadas com a versão em espanhol do Inventário de Depressão de Beck e do Inventário de Ansiedade de Beck, respectivamente. A resiliência psicológica foi avaliada com a escala mexicana específica para essa variável. A referida pesquisa encontra associações da resiliência com depressão e ansiedade em pacientes com DRC, sugerindo que a resiliência pode funcionar como um fator de proteção contra esses sintomas. A depressão foi avaliada em 76% e a ansiedade em 60%.

V. Conclusões

Na literatura sobre os pacientes hemodialíticos não foi encontrada pesquisa que tenha realizado associações entre o autocuidado com a FAV e as quatro variáveis em foco – resiliência, depressão, estresse e ansiedade.

Os gráficos demonstraram que na análise de associação com os escoresdos formulários de Resiliência e o DASS, em relação ao FAV Geral, nenhum deles demonstrou haver associação estatisticamente visível.

Considerando-se as quatro variáveis mensuradas, nossa pesquisa apontou a ansiedade como predominante, o que contrasta com a constatação de que na literatura a depressão é apontada como o sintoma mais frequente. As referências ao autocuidado aparecem de modo esparso na literatura, assim como alguns estudos mencionam que o enfermeiro deve encaminhar os pacientes hemodialíticos depressivos para profissionais da área da saúde mental.

Durante a aplicação das escalas DASS e CD-RISC, percebemos que a maioria dos participantes respondiam especificamente estas escalas tentando não serem estigmatizados.

VI. Limitações do Estudo

O estudo apresentou algumas limitações que devem ser consideradas na interpretação dos resultados. Por fim, apesar das análises realizadas, não

foram encontradas associações estatisticamente significativas entre os desfechos psicológicos, como ansiedade, depressão, estresse e resiliência, e os comportamentos de autocuidado, o que sugere a necessidade de investigações futuras para melhor compreender essa relação.

VII. Contribuições do Estudo

Este estudo oferece contribuições relevantes para a compreensão da saúde mental de pacientes com fístula arteriovenosa (FAV) em hemodiálise, especialmente no que diz respeito à prevalência da ansiedade, depressão e estresse nesse grupo. Os achados indicam que a ansiedade foi o transtorno psiquiátrico mais frequente, afetando 52,83% dos participantes, enquanto a depressão e o estresse também apresentaram índices elevados. Esses resultados são importantes, pois contrastam com a literatura vigente, que geralmente aponta a depressão como o transtorno mais prevalente em pacientes hemodialíticos.

Além disso, o estudo reforça a necessidade de um olhar mais atento dos profissionais de saúde para a saúde mental desses pacientes, visto que sintomas emocionais podem impactar diretamente o tratamento e a qualidade de vida. A pesquisa também destaca a importância da resiliência como um fator presente no enfrentamento da doença, sugerindo que intervenções voltadas para o fortalecimento desse aspecto podem ser benéficas.

Outra contribuição relevante é a ausência de associações estatísticas entre os indicadores de saúde mental e os comportamentos de autocuidado. Esse achado levanta questionamentos sobre a influência de outros fatores, como suporte social e adesão ao tratamento, na relação entre saúde emocional e manejo da doença. Por fim, ao comparar seus resultados com estudos internacionais, a pesquisa amplia a discussão sobre as particularidades da ansiedade e da depressão no contexto da hemodiálise, abrindo espaço para novos estudos e estratégias de cuidado voltadas para esse público.

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Knowledge, Attitudes, and Barriers to Mammogram Screening among Northern Saudi Women: A Population-based Cross-Sectional Study

By Kazi Mahmudul Hasan, Manjusree Mitra, Jannatul Ferdousi & Lamia Kabir

University of Kinshasa

Abstract- Mammogram screening (MS) is the most effective method for the early detection of breast cancer (BC), yet uptake of MS is low in Saudi Arabia, especially in traditional regions. This cross-sectional study examined 400 women in Aljouf Province in Saudi Arabia from September 2022 to February 2023 regarding BC knowledge, attitudes toward MS, and perceived barriers to participating in MS. Of the women surveyed, 56.3% had low to medium levels of knowledge of BC, which was significantly related to higher education levels and a history of BC in the family. Most notable barriers to participating in MS included fear of BC diagnosis (50.8%), fear of examination procedures, and cultural issues, notably, becoming embarrassed.

Keywords: *breast cancer, mammogram screening, Saudi Arabia, knowledge, barriers, public health, conservative societies.*

GJMR-K Classification: *NLMC: WP 870*

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Abstract- Mammogram screening (MS) is the most effective method for the early detection of breast cancer (BC), yet uptake of MS is low in Saudi Arabia, especially in traditional regions. This cross-sectional study examined 400 women in Aljouf Province in Saudi Arabia from September 2022 to February 2023 regarding BC knowledge, attitudes toward MS, and perceived barriers to participating in MS. Of the women surveyed, 56.3% had low to medium levels of knowledge of BC, which was significantly related to higher education levels and a history of BC in the family. Most notable barriers to participating in MS included fear of BC diagnosis (50.8%), fear of examination procedures, and cultural issues, notably, becoming embarrassed. A negative correlation was observed between barriers and knowledge; for instance, higher knowledge of BC was related to perceived fewer barriers to MS. In summary, it is important to take a multi-faceted approach to address the deficits in knowledge related to BC and consider culturally sensitive education, improved communication regarding healthcare, and programs aimed at providing better screening measures. Future multicentric studies are suggested to account for the possible qualitative barriers to MS.

Keywords: breast cancer, mammogram screening, saudi arabia, knowledge, barriers, public health, conservative societies.

I. Introduction

Breast cancer (BC) is the leading neoplastic condition of women globally, and in 2022 had almost 2.4 million new diagnoses and 685,000 deaths, the leading cause of cancer-related death in women in 157 out of 185 countries [1]. Morbidity is predominantly important in developed nations where 1 out of 12 women will get BC in her lifetime, though more than 90% survival if detected early [2]. On the other hand, low Human Development Index (HDI) LMICs have incommensurately elevated rates of BC mortality, where 1 woman dies out of 48 due to BC in comparison to 1 woman dying out of 71 in wealthy countries [3]. By 2040, projections anticipate a 40% increase in new BC cases to over 3 million annually, with deaths potentially rising from 685,000 to 1 million, driven by LMICs' population aging, lifestyle changes, and limited access to screening and treatment [1]. Interestingly, over 70% of new BC cases and 81% of deaths occur in women aged over 50, for whom targeted screening among them is therefore vitally necessary [4].

In the Kingdom of Saudi Arabia (KSA), BC is the leading cancer in women, reflecting global trends but augmented by region-specific determinants such as increasing obesity, physical inactivity, and cultural shift towards Westernized lifestyles [5]. The KSA Ministry of Health (MOH) has adopted stringent policies to fight this burden and provides free mammogram screening (MS) to women between 40–50 years every two years and annually or biennially to women between the ages of 51–69 years, with earlier screening advised in women with a family history of BC [6]. Mammography continues to be the gold-standard method for early BC detection, proven to reduce mortality through facilitating timely intervention and reducing treatment costs [7]. Poor uptake of MS has, however, been documented by epidemiological surveys, particularly in conservative regions like Aljouf Province, where modesty and privacy aspects dominate disengagement [8].

MS cultural and psychological barriers are not unique to Saudi Arabia but cross other conservative societies, such as Bangladesh, where 20,000–30,000 new BC cases and 13,000 deaths present annually [9]. In Bangladesh, 80% of patients with BC die due to late presentation, usually by greater than six months' delay, and 70% of presentations involve alternative therapies such as homeopathy before receiving allopathic treatment [9]. These universal obstacles in these environments include shyness, fear of diagnosis, mistrust of the health system, and a culture that prioritizes family responsibilities over individual health [10]. Parallel obstacles-fear of BC diagnosis, shame during investigations, and inadequate communication from the health sector-exist in Saudi Arabia, as do issues of prolonged waiting lists and taking work leave [8,11].

At the international level, awareness of BC mortality is high, with poor knowledge about risk factors

Author α σ ρ: Department of Public Health, Canadian University, Bangladesh. e-mail: mahmud1206028@gmail.com
Author ω: Popular Medical College, Bangladesh.

and screening, particularly among Asian and African women compared to Western women [12]. For instance, a study conducted in New Delhi, India, reported 50% awareness of BC component among women, with only 7% who had utilized MS, the majority of which was attributed to low socioeconomic status and education levels [13]. In Malaysia, high-risk profiles are seen in only half of eligible women for MS, with higher uptake observed among older women and those counseled by physicians [14]. This emphasizes the role of education, as well as access to healthcare, in enhancing screening rates.

Even though MS is available for free, Saudi Arabia has not started MS use widely, so it is important to find out what is getting in the way and what is misunderstood. This research looks at northern Saudi women aged 40–69 in Aljouf, a place known for its conservatism, and where little is known about how BC is screened. Gathering information about BC risk factors, attitudes toward MS, and perceived barriers is meant to help this study find out what influences low MS use and then suggest targeted actions to deal with them. What we learn from this research can be relevant to other conservative countries like Bangladesh, since they share the same cultural and systemic challenges, supporting global steps to decrease BC risk by applying better screening measures.

II. Methodology

a) Study Design and Setting

From September 2022 to February 2023, the research was carried out throughout Aljouf Province in northern Saudi Arabia. Being one of KSA's conservative provinces, Aljouf provides an advantageous setting to research why women in this region avoid getting mammograms. A cross-sectional design was selected because it provides one instant view of knowledge, attitudes and barriers, making it both affordable and easy to use for creating and checking hypotheses and estimating how common these problems are in the population. It is useful for this study since not many data are available on BC screening routines in Aljouf. The study was limited to Saudi women aged 40–69, matching the MS guidelines from the KSA Ministry of Health (MOH) which prescribe screening in this age group [6]. It was necessary for participants to be Saudi, have access to life in Aljouf, be able to read and write Arabic and willingly give informed consent. To be sure the sample was the same as the community, expatriates, non-residents of Aljouf and women who couldn't complete the questionnaire due to language or reading problems were excluded.

b) Sampling

We estimated the sample size using Cochran's equation for large populations, a method regularly applied in epidemiological studies to avoid small samples [16]:

$$n_0 = \frac{Z^2 pq}{e^2}$$

Where:

- n_0: Sample size
- Z: Z-score corresponding to the desired confidence level (1.96 for 95% confidence)
- p: Estimated proportion of the attribute in the population (set at 0.5 to assume maximum variability, as no prior data on MS uptake in Aljouf were available)
- q: (*1-p*) (0.5)
- e: Margin of error (0.05 for 5%)

To meet these parameters, a minimum of 385 sample participants was needed. This figure was increased to 400 since some people may not respond or finish their questionnaires. Since there is high variation in learning and access to MS in heterogeneous populations, the Cochran formula was chosen [16]. Eligible women were recruited using convenience sampling, which is easy in places such as parks, shopping malls, and mosques. We invited every 10th woman to join the study to aid in diversifying the group by age, education, and socioeconomic status. Those recruited were introduced to the study by trained research assistants with Arabic skills who presented the same information about it.

c) Data Collection

An approved Arabic-language form, originally developed by Abdel-Salam et al. [8], was employed to gather the data and was checked in a pilot with 30 women from Aljouf. Small changes to explain medical jargon in simpler language were made to fit readers with different educational levels. The three sections of the questionnaire included: (1) sociodemographic factors (age, marital status, education, employment status, income, place of residence and family background with BC); (2) knowledge of BC and MS health education (14 items); and (3) perceived barriers to MS (e.g., fear of cancer, diagnosis, pain, radiation, embarrassment, constraints related to work or family and dissatisfaction with healthcare communication, indicated by 19 statements). An easy-to-understand 5-minute guide on BC, MS, and the objectives of the study was provided to every participant, with trained female assistants on hand to help them answer the 15–20-minute questionnaire without a name.

d) Data Analysis

All statistical analyses were completed with SPSS version 21, from the IBM Corporation in Armonk, NY, USA. Lots of care was given to the first round of data cleaning, resulting in only 2% of responses on some Likert-scale items needing to be filled in using the

mean. Results for frequencies and percentages were reported for all participants' characteristics, knowledge levels and responses. Applying the Shapiro-Wilk test, we found that data lacked normal distribution (with a P-value of less than 0.05), allowing us to proceed with non-parametric statistical analyses.

Spearman correlation test was applied to analyze how learning changes correlate with the perceived recognition and learning barriers scores and rho was used to describe the type and intensity of the correlation. The knowledge scores from the survey were changed to a binary grouping of high and low or medium, to find out what helps people remember the benefits of cervical cancer. The independent variables we used were age, education, marital status, income, residence and if the person had a family history of BC. To overcome confounding, we relied on aORs matched with 95% CIs after correcting for important factors such as education and family history, as noted in the scientific literature [12]. We considered results to be statistically significant when $P<0.05$ with two-tailed tests. For this analysis, model fit was confirmed by testing it with the Hosmer-Lemeshow test ($P>0.05$), which stated the model is suitable for fitting the data.

e) Ethical Considerations

The ethics committee of Qurayyat Health Affairs at the KSA MOH (registration number H-13-S-071) approved the study protocol and confirmed it followed the Declaration of Helsinki [18]. Candidates received a clear explanation of the study's aims, the importance of BC, and what MS tests involve. A written form of informed consent told everyone about their rights, including the right to leave anytime they like. Personally identifiable information was not gathered since all questionnaires were anonymized. All data were kept on password-protected devices that only members of the research team could access. Using women as assistants and interviewing in private, away from family, made it less awkward for participants to talk about birth control.

III. Results

a) Participant Characteristics

Two hundred and thirty-three (58.3%) of the 400 women in the survey were between 40 and 49 years old, 351 (87.8%) were married, and 266 (66.5%) had a university-level education. Insufficient income was felt by 237 (59.3%) of the individuals who had less than 7,000 Saudi Riyals monthly (23,874.5 USD annually), and 163 (40.7%) reported monthly earnings of over 7,000 SAR. The majority of participants (341 people or 85.3%) lived in urban areas, and 49 (12.3%) reported having relatives with breast cancer as shown in Figure 1. Among the 400 people, 192 (48.0%) were working, and the rest were unemployed or kept home. Most participants live in urban areas and have at least some educations, yet some rural participants (14.7%) shared information from Second Amendment organizations based in their communities.

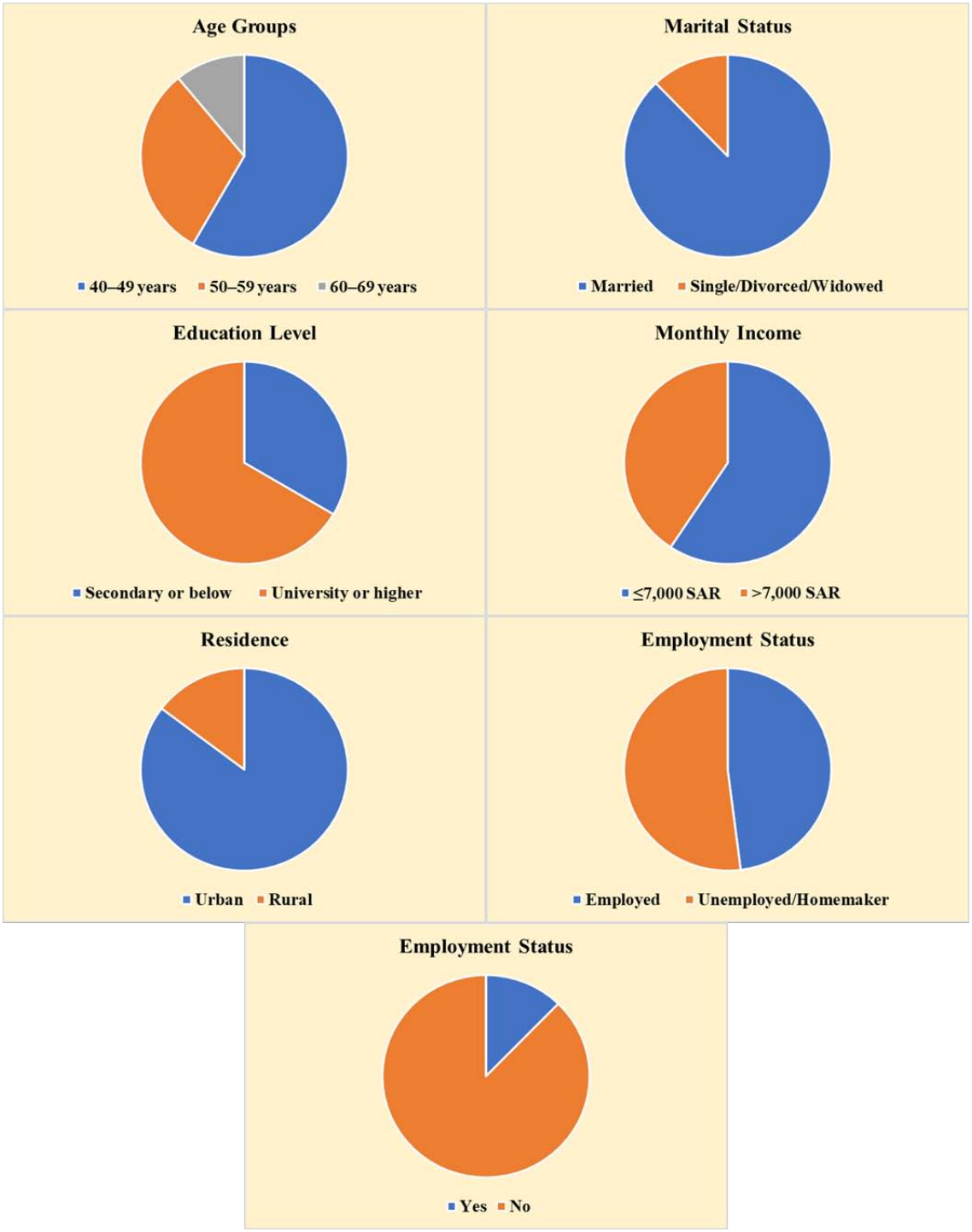

Figure 1: Sociodemographic Characteristics of Participants (N=400)

b) Knowledge of BC and MS

14 questions were used to measure knowledge of BC risk factors, and the most common risks named by participants included smoking, having unhealthy eating habits, having a family history, and getting older. Other less well-known risks were obesity (reported in 171 or 42.8%), low levels of physical activity (noted in 158 or 39.5%), and earlier menarche (found in 132 or 33.0%). Almost half of those surveyed (46.8%) knew that MS is the main tool for early BI detection, but only 40.0% realized they could receive free MS as per KSA MOH directions. Using the cut-offs from Bloom's taxonomy, 135 learners (33.8%) had low knowledge, 90 (22.5%) had medium knowledge, and 175 (43.8%) had high knowledge. A total of 225 (56.3%) had limited knowledge of the subject, which is a substantial gap in this group.

c) Barriers to MS Uptake

The top three reasons people didn't get MS were fear of BC, worry about what the tests could involve, and not knowing much about MS (203, 50.8%; 176, 44.0%; 163, 40.8%). Other serious difficulties for respondents were not enough time (142, 35.5%), feeling embarrassed during breast exams (129, 32.3%), poor explanations from medical staff (112, 28.0%) and logistical hurdles like very long waiting times (94, 23.5%) and difficulty off from work (87, 21.8%). Living away from screening services was a bigger problem for rural participants (54.2%) than urban participants (18.2%). The totals for barrier scores were classified as being low (180, 45.0%), medium (136, 34.0%), or high (84, 21.0%), with a mean of 19.8 and a standard deviation of 7.2. Figure 1 shows the breakdown of primary obstacles.

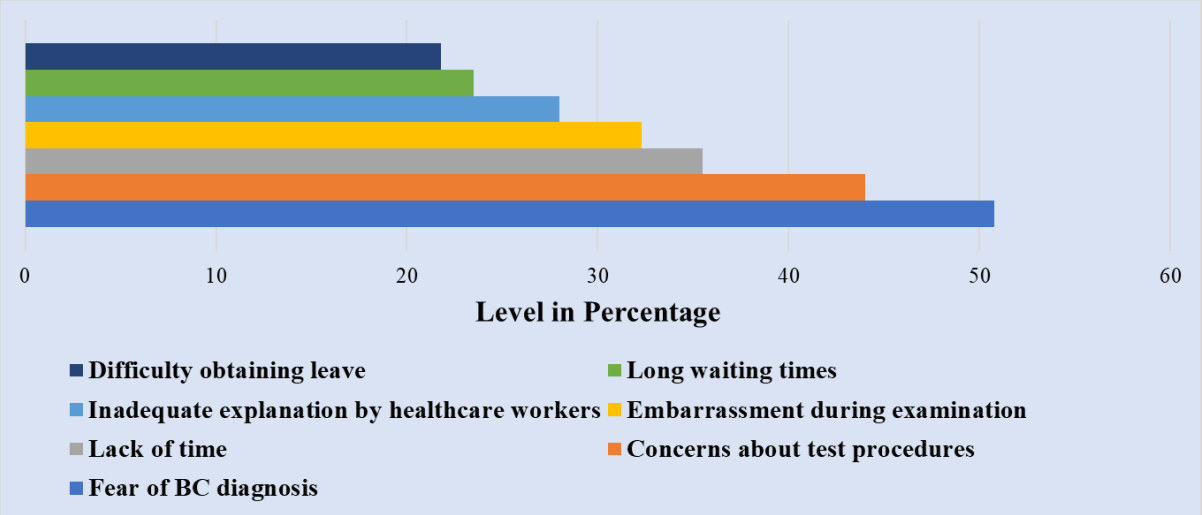

Figure 2: Primary Barriers to Mammogram Screening Uptake

d) Statistical Associations

Binomial logistic regression modeling found important factors associated with high scores in local knowledge. Those with university-level education had a higher chance (nearly 2.5 times) of high knowledge than those with secondary education or less (aOR 2.35; 95% CI 1.61–3.13; P=0.008). BC family history was linked to a 3.66 higher risk among those with good knowledge (aOR, 3.66; 95% CI, 1.94–5.49; P<0.001). Age, marital status, income and residence (P=0.214, P=0.387, P=0.162, P=0.091) did not predict whether the disease was present. There was a good match between the model predictions and actual results (Hosmer-Lemeshow test with a P-value of 0.672). It was found that there was a significant negative connection (rho=-0.389, P<0.001) between how much people know and how many perceived barriers. The assessment showed rural participants scored lower on knowledge (mean=8.2, SD=2.9) than urban participants did (mean=9.7, SD=3.1) in terms of p-values (P=0.012).

IV. Discussion

Results of this study show that northern Saudi women report various knowledge gaps and more than half (56.3%) have low to average understanding of BC risk and MS. Better awareness and higher education are strongly related (aOR, 2.35; 95% CI, 1.61–3.13) and this is supported by research from all over the world [11,12]. Specifically, Saeed et al. observed that those Pakistani women with a tertiary education were better informed about BC than women with less schooling [19]. In the same way, having a family history of BC made subjects better informed (aOR, 3.66; 95% CI, 1.94–5.49), possibly from direct exposure to the disease, as also seen by Akhigbe et al. with cases in Nigeria [23]. Knowledge and barriers to screening are negatively correlated (rho=-0.389, P<0.001), implying that women who are knowledgeable about screening see lower barriers, which has been noted in India and Malaysia [14,20].

Most participants stated that avoiding a BC diagnosis because of fear (reported by 50.8%) mainly showed the strong psychological and cultural concerns that exist in conservative societies. Because modesty and privacy are important in Saudi Arabia, women often find embarrassment when they have to have their breasts examined (32.3%), as past studies have pointed out (8). In Bangladesh, it is found that 70% of women postpone diagnosis by over three months because of fear, timidity, and cultural beliefs about family duties [9]. Most patients with BC in Bangladesh lose their lives after their cancer has advanced, often because they relied on homeopathy before turning to traditional health services [9]. Test methods (scans and needles) are bothersome, so they refuse to get checked, much as D'almeida et al. found in India, with 57% of women saying the same thing [10]. When healthcare workers do not communicate well enough (28.0%), global studies point out that spreading clear information encourages individuals to take part in screening [21].

More participants from rural areas had less knowledge and reported higher hurdles like living far from medical services (54.2% of cases) compared to urban participants. This is consistent with what happens globally in LMICs, as rural residents struggle more to obtain healthcare [3]. In comparison, the United Kingdom has a lower rate (82%) because the campaign isn't as strong and screening isn't easily accessible [22]. Based on Saudi Arabia and Bangladesh, it is evident that there is a need for healthcare approaches that fit conservatism and that aim to resolve fears about modesty by providing mobile services and female-led teams.

It is notable that this study had a large enough sample, the size of which was calculated using Cochran's formula and it used a questionnaire that is reliable (Cronbach's alpha=0.82). Being able to estimate numbers of cases is cheap, but the design makes it hard to tell if there is a link between knowledge and barriers. The results for Aljouf might be different in other KSA regions where the culture or socioeconomics are not the same. Biases, for example, remembering events differently or picking volunteers easily available, can skew the study's outcomes. When surveys are held in public, the women studied are usually from cities or can move easily, perhaps leaving out those who live in more remote areas. In the future, both interview-based research and studies including many sites should be used to better understand cultural and psychological barriers in such societies and make the findings general.

It is clear from these findings that special interventions are needed to improve MS uptake. Such interventions should include targeted education, highlight lifestyle risks and stress early screening using culturally appropriate workshops run by female healthcare professionals. Training should help healthcare professionals explain benefits and risks of MS with empathy, reduce worries about discomfort and radiation, and use models known in nations with top MS practices. Increasing access using mobile screening, flexible schedules, easier ways to get there, or screenings at the workplace is very important for those living in rural areas. Program developers should learn from places like Sweden and introduce information campaigns and a unified BC screening process. Moreover, making connections with local leaders and mosques allows highlighting MS and finding solutions that address ways modesty is often seen as a barrier by many communities. Such strategies could also be used in other conservative societies like Bangladesh, as the same barriers stop early detection there. For instance, 70% of BC cases in Bangladesh are detected in private hospitals, and only 5% of the public is aware of mammograms. This underlines that universal BC prevention and health care programs are important in Bangladesh [9].

V. Conclusion

This research shows that both low understanding and tough barriers, for example, fear and related cultural issues, make it harder for northern Saudi women to access MS. The amount of information one knows about BC is mainly influenced by education and family history, and understanding at the HEP level tends to go up as challenges decline. The KSA MOH and health workers should offer appropriate guidance campaigns, strengthen connections, and secure equitable and culturally fitting screening programs for MS. Further mixed-methods studies that cover different areas should be done to understand qualitative barriers that might lead to new national strategies applicable in other conservative societies, such as Bangladesh.

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Hereditary Hemochromatosis: Clinical and Metabolic Disorders

By Ana Luiza Alvarenga, Andressa Lourenço Carvalho, Nathalia Izabelle Alves da Silva, Bianca Calciolari, Rafael Shoiti Nagao, Alysson Ribeiro Martins & Daniel Moreno Garcia

Universidade Anhembi Morumbi

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Hereditary Hemochromatosis: Clinical and Metabolic Disorders

Hemocromatose Hereditária: Distúrbios Clínicos E Metabólicos

Ana Luiza Alvarenga [α], Andressa Lourenço Carvalho [σ], Nathalia Izabelle Alves da Silva [ρ], Bianca Calciolari [ω], Rafael Shoiti Nagao [¥], Alysson Ribeiro Martins [§] & Daniel Moreno Garcia [χ]

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Palavras-Chave: Hemocromatose. ferro. hepcidina. henética. hiagnóstico precoce.

I. Introdução

A hemocromatose hereditária (HH) é uma doença caracterizada como autossômica recessiva, cujo mecanismo fisiopatológico se dá por um excesso de ferro circulante no organismo e, consequentemente, formação de depósitos desse metal em diferentes órgãos e tecidos. Sua primeira descrição na literatura como uma doença de ordem genética foi associada a variantes no gene HFE, que codifica a proteína do tipo MHC-I de mesmo nome originado da expressão em inglês “High Fe”, aludindo ao acúmulo de ferro no organismo dos indivíduos acometidos pela doença[1]. Esse acúmulo de ferro no organismo gera sinais e sintomas ao paciente de forma sistêmica, além do quadro hepático, principal alvo da doença. Dessa forma, a HH deve ser elucidada para um bom prognóstico e tratamento precoce[2].

A HH é um distúrbio mais comum em brancos, sua incidência varia entre os lugares do mundo, pode chegar de 1,5 a 3 casos por 1.000 pessoas até 1 caso por 200-400 pessoas, mas como só pode ser avaliada na triagem neonatal, sua incidência é difícil de ser determinada[3]. Outrossim, HH é mais frequente em descendentes da Europa Setentrional, principalmente irlandeses e noruegueses, mas é menos comum em descendentes de Asiáticos e Africanos.

Nota se que a HH tipo 1 é observada principalmente em pessoas descendentes do norte da Europa e a tipo 2, 3 e 4 no resto do mundo[3]. Os homens são mais afetados que as mulheres (3:1), principalmente os que possuem idade superior a 50 anos[4]. Nota-se que a mutação mais presente é no gene C282Y, mas apenas 10% dos indivíduos que possuem essa mutação apresentam manifestações clínicas ou lesões de órgãos-alvo. Os homozigotos para mutação C282Y representam aproximadamente 85 a 90% das pessoas com HH.[1] Os homens que possuem essa mutação manifestam sintomas relacionados à deposição tecidual de ferro mais comumente do que as mulheres, pois possuem uma penetrância bioquímica e clínica maior. Além disso, mulheres com hemocromatose tornam-se sintomáticas mais tardiamente, devido à perda de sangue e consequente excreção de ferro associada à menstruação. [3]

II. Objetivo

O principal objetivo desta revisão de literatura é fazer um compilado de informações disponíveis sobre a hemocromatose hereditária, desde suas bases genéticas patológicas até o tratamento.

Author α σ ρ ω ¥ §: Discente do Curso Superior de medicina da Universidade Anhembi Morumbi Campus Mooca.
e-mails: analualvamed@gmail.com, a.l.c.andressa.l.c@gmail.com, alvesnath.ias@gmail.com, biancacalciolari@gmail.com, rafa11nagao@gmail.com, alysson.rmartins@outlook.com
Author χ: Coordenador de Curso Superior de Ciências Biológicas e Saúde da Universidade Anhembi Morumbi Campus Mooca, Vila Olímpia. Mestre em Biotecnologia pela Universidade de Mogi das Cruzes e Doutor em Ciências (Farmacologia) pela Universidade Federal de São Paulo. e-mail: danielm-g@hotmail.com

III. Metodologia

A revisão de literatura vigente foi realizada com a base de dados Pubmed utilizando as palavras-chave "hemochromatosis", "disturbed homeostasis", "iron overload", "homeostasis", "metabolism", "hereditary hemochromatosis" com o número inicial de 68 artigos, que passaram por rigorosa seleção, alcançando o número final de 27. Foram critérios de inclusão: artigo em língua inglesa ou portuguesa, condizente com a temática do artigo, que inclui mecanismo molecular e genético. Critérios de exclusão: artigos em outras línguas, que não contemplam o tema abordado no artigo. Além dos artigos selecionados, foram utilizadas outras referências como forma de complementação do texto.

IV. Resultados e Discussões

As mutações inicialmente destacadas na HH eram ambas do tipo *missense*, sendo a mais comum uma troca de nucleotídeo que resultava na substituição de cisteína por tirosina (Cys282Tyr), seguida por uma substituição de histidina por aspartato (His63Asp) que, além de menos frequente, também possui menor penetrância gênica[1,5]. A proteína HFE é uma das responsáveis pela regulação da hepcidina, peptídeo que controla os níveis ferro ao impedir que enterócitos liberem o ferro adquirido na dieta para a corrente sanguínea e que macrófagos liberem o ferro adquirido na eritrofagocitose por meio de sua interação com a ferroportina que, em vez de permitir a passagem do ferro, é internalizada e degradada. Portanto, quanto menor o nível de hepcidina, maior será a concentração plasmática de ferro[6]. Todavia, a proteína HFE não é a única ferramenta que o organismo utiliza para determinar a quantidade de hepcidina que é necessária para manter a homeostase e, por esse motivo, a hemocromatose hereditária pode ser causada por mutações em outros genes, como HJV, que corresponde à hemojuvelina, também controla a liberação da hepcidina; HAMP, que codifica a hepcidina em si; e TFR2, responsável pelo receptor da transferrina. Esse tipo de caso, chamado de hemocromatose não HFE, é mais raro e tende a apresentar um quadro clínico mais severo, inclusive com manifestação de sintomas ainda na juventude[6,7]. Pode ainda ocorrer ganho de função no gene SLC40A1 (ou FPN1), dessa vez uma mutação dominante, deixando a ferroportina resistente à hepcidina e concomitante a altos níveis de ferritina[8,9]

Considerando tais variações, é possível dividir a hemocromatose em subtipos: tipo 1 (associado ao HFE), tipo 2A (associado ao HJV), tipo 2B (associado ao HAMP), tipo 3 (associado ao TRF2) e tipo 4 (associado ao SLC40A1)[6]. No comprometimento funcional desse sistema regulatório, apesar das diferentes vias a depender da mutação do indivíduo, a hepcidina reduzida culmina em um aumento do exporte de ferro dos enterócitos e macrófagos para o plasma. Através disso, é possível compreender como a patologia se desenvolve. A nível microscópico, o tecido sofre com inflamação, fibrose, dano celular e ferroptose, além de um risco maior de desenvolver infecções e até mesmo neoplasias [10].

A deposição de ferro no fígado se deve principalmente à absorção que os hepatócitos realizam de espécies de ferro não ligadas à transferrina, fazendo com que ele seja o órgão mais afetado por seu excesso no organismo[11]. O quadro hepático costuma demorar décadas para se desenvolver em casos típicos, mas tende a progredir para um quadro de cirrose, especialmente em pacientes com a ferritina acima de 1000 ng/mL. Hepatoesplenomegalia, ascite e carcinoma hepatocelular também são manifestações dos efeitos da hemocromatose associadas ao fígado[12]. Indivíduos homozigotos para a mutação em HFE podem ter desfechos clínicos diferentes, a depender de fatores como estilo de vida (etilismo, dieta, hepatites virais) ou ainda a presença de heterozigose para outro gene envolvido no controle da absorção do ferro de forma direta ou indireta[13]. Em relação às espécies de ferro não ligadas à transferrina, o coração e o pâncreas também são órgãos afetados de uma maneira particular: os cardiomiócitos possuem uma suscetibilidade a absorver essa conformação específica do metal, tendo sua atividade prejudicada, enquanto as células acinares e as células-β pancreáticas são as mais afetadas. Por isso, miocardiopatia com disfunção diastólica, insuficiência cardíaca, arritmias e diabetes mellitus podem ser complicações da hemocromatose hereditária[14,12].

De maneira sistêmica, a hemocromatose também é capaz de causar hiperpigmentação da pele (chamada de diabetes bronzeado), aranhas vasculares (por causa do fígado cirrótico), hipogonadismo (por acúmulo de ferro na hipófise, associado a amenorreia, impotência sexual, atrofia testicular e infertilidade), hipotireoidismo, dor abdominal, osteoporose, osteoartrite, artralgia e fadiga, sendo os dois últimos sintomas os mais frequentemente relatados[15,16,4].

Os sintomas e sinais tendem a estar ausentes durante as primeiras décadas de vida, especialmente na forma da doença associada a HFE, aparecendo por volta da terceira e quarta década de vida para homens e entre a quarta e quinta para mulheres, no período pós menopausa[6]. Tal diferença é explicada pela menstruação como um fator de proteção, o que diminui a velocidade de acúmulo de ferro através da sua eliminação constante e resultando em sintomatologia mais branda[16]. Os tipos 2A e 2B de hemocromatose hereditária (ligados a HJV e HAMP, respectivamente) tendem a ter manifestações clínicas graves entre a primeira e terceira décadas de vida, incluindo fibrose e

câncer hepático, diabetes mellitus e insuficiência cardíaca[17].

O diagnóstico pode ter início por meio da dosagem sérica da saturação de transferrina ou da concentração de ferritina. Nesse sentido, os valores que corroboram com a hipótese de hemocromatose incluem: um nível de ferritina maior que 200mcg/L em mulheres ou 300 mcg/L em homens e/ou uma saturação de transferrina superior a 40% em mulheres e 50% em homens[3]. Considerando a presença das alterações laboratoriais supracitadas, pode-se solicitar teste genético, uma vez que a hemocromatose hereditária tipo 1 é causada por mutações do gene HFE. Dessa forma os testes genéticos devem averiguar a presença de mutações homozigóticas C282Y e H63D[4]. Sabe-se que esses testes genéticos são capazes de confirmar o diagnóstico de aproximadamente 90% dos casos da doença e em caso de confirmação torna-se preciso fazer a triagem dos parentes de primeiro grau dosando os níveis séricos de ferritina e pesquisar se há mutações no gene HFE[3].

Cabe citar que o paciente pode apresentar testes negativos para sobrecarga de ferro nos alelos C282Y e H63D. Nesse caso pode-se considerar a hipótese de hemocromatose do tipo 2,3 e 4, entretanto não são recomendados testes genéticos adicionais como rotina[4]. Exames de imagem como radiografia, ressonância magnética e ecocardiografia podem ser utilizados para evidenciar lesões nos órgãos envolvidos, como presença de cardiomegalia e fibrose hepática[4]. Para avaliar a extensão do dano hepático, é possível realizar uma biópsia do fígado, recomendada em casos de elevação das enzimas hepáticas em pacientes diagnosticados com hemocromatose e/ou em pacientes com o nível de ferritina sérica maior que 1000mcg/L[3].

V. Conclusão

É necessário entender que a HH não possui cura, e o tratamento gira em torno da retirada do excesso de ferro de forma constante. Cabe ao médico o cuidado específico em relação às lesões dos órgãos afetados e em muitos casos a recomendação do aconselhamento genético, para melhor compreensão da doença, do manejo, das complicações e tratamento precoce[16].

Diante disso, a flebotomia, também conhecida como sangria terapêutica, é a principal conduta tomada na HH, descrita pela primeira vez há mais de 70 anos e usada até hoje. É um processo que realiza a retirada do sangue do paciente por meio de uma técnica semelhante à doação de sangue convencional. Esse tratamento visa alcançar uma concentração da ferritina sérica de 50 ng/mL até 100 ng/mL e aumentar a viscosidade sanguínea nas eritrocitoses, tomando cuidando e sempre monitorando a hemoglobina para não ficar menor que 11g/dL[4]. Esse procedimento segue entre o período de coleta e a quantidade de sangue retirada de acordo com o paciente e sua porcentagem de ferro, objetivando a diminuição da fadiga, da letargia e da hiperpigmentação da pele causada pelo excesso de ferritina e alta taxa de saturação da transferrina sérica. Além disso, previne quadros hepáticos, complicações em casos de pacientes sintomáticos com danos aos órgãos sofridos pelo excesso de depósito do metal, e o gerenciamento e controle do diabetes, melhora na função cardíaca e dor abdominal[18].

Em relação a dieta, ela pode ser mantida pois não há acréscimo exagerado no nível de ferro. Por outro lado, as suplementações que possuem vitamina C devem ser evitadas, já que o ácido ascórbico aumenta a absorção de ferro. Suplementações com o metal e consumo de álcool também devem ser evitados[4].

Estudos mostram alguns procedimentos alternativos à flebotomia, que é o caso da eritrocitaférese e quelação. Sobre a primeira, corresponde a técnica que remove seletivamente as hemácias e devolve ao paciente alguns componentes, como proteínas plasmáticas, fatores de coagulação e plaquetas. A terapia é individualizada, sendo indicada principalmente para pacientes que sofrem de hipoproteinemia ou trombocitopenia[16,3]. Já a quelação, satisfaz um tipo de tratamento farmacológico que envolve o sequestro de íons de ferro, que costuma ser usado em casos de hemocromatose eritropoiética ou em pacientes com alguma imunodeficiência. O deferasirox é o principal quelante de ferro, administrado por via oral, excreta o ferro por meio da urina e possui como efeitos colaterais desconfortos gastrointestinais e sintomas articulares. Outro exemplo de quelante utilizado, de custo mais elevado e menos eficaz em comparação ao deferasirox, é o deferoxamina (DFO) administrado por via subcutânea e possui como efeitos colaterais infecções por *Yersinia sp* e lesões retinianas[3,19].

Muito se discute sobre a possibilidade de doação desse sangue coletado durante a flebotomia terapêutica. A justificativa inclui a preocupação em relação a transmissão de certas infecções siderófilas, patógenos transmitidos pelo sangue e toxicidade do ferro não ligado a transferrina. Contudo, estudos apontam que o sangue de doadores HH não parece surtir riscos infecciosos transmissíveis em comparação ao controle[20].

De acordo com a Resolução - RDC Nº 222, DE 28 DE MARÇO DE 2018 da Agência Nacional de Vigilância Sanitária (ANVISA) que regulamenta as boas práticas de gerenciamento dos resíduos de serviços de saúde e de outras providências, a prática de flebotomia se encaixa no subgrupo A1 do grupo A de classificação dos resíduos de serviços de saúde, ou seja, fazem parte das bolsas transfusionais contendo sangue ou hemocomponentes rejeitadas por

contaminação ou por má conservação, ou com prazo de validade vencido, e aquelas oriundas de coleta incompleta, devendo ser acondicionadas em saco vermelhos de acordo com o Art.16. Após isso, deve ser descartado diretamente no sistema de coleta de esgotos, seguindo atentamente as normas estabelecidas pelos órgãos ambientais, gestores de recursos hídricos e de saneamento competentes. No Brasil, a doação de sangue retirado na flebotomia não é permitida.

Conclui-se, dessa forma, que a ferritina sérica é um achado clínico na hemocromatose hereditária, e também comumente encontrado em outras etiologias. Todas as mutações presentes na literatura parecem ter em comum a baixa penetrância para sobrecarga de ferro, o que cumila no acúmulo desse metal em tecidos que comprometem a homeostasia fisiológica do paciente[20]. É imprescindível que, com testes diagnósticos apropriados, os pacientes com HH possam ser identificados com precisão e encaminhados para tratamento multiprofissional, com intuito de prevenir complicações futuras em órgãos-alvo.

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The primary objective is to recognize the leaders in research and scientific fields of the current era with a global perspective and to create a channel between them and other researchers for better exposure and knowledge sharing. Members are most eminent scientists, engineers, and technologists from all across the world. Associate membership can later be promoted to Fellow Membership. Associates are elected for life through a peer review process on the basis of excellence in the respective domain. There is no limit on the number of new nominations made in any year. Each year, the Open Association of Research Society elect up to 12 new Associate Members.

Benefits

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Career | Financial

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Career | Credibility | Reputation

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Financial

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Associates are authorized to organize symposium/seminar/conference on behalf of Global Journal Incorporation (USA). They can also participate in the same organized by another institution as representative of Global Journal. In both the cases, it is mandatory for him to discuss with us and obtain our consent. Additionally, they get free research conferences (and others) alerts.

Career | Credibility | Financial

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Exclusive | Financial

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Associate	Fellow	Research Group	Basic
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Preferred Author Guidelines

We accept the manuscript submissions in any standard (generic) format.

We typeset manuscripts using advanced typesetting tools like Adobe In Design, CorelDraw, TeXnicCenter, and TeXStudio. We usually recommend authors submit their research using any standard format they are comfortable with, and let Global Journals do the rest.

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Authors should submit their complete paper/article, including text illustrations, graphics, conclusions, artwork, and tables. Authors who are not able to submit manuscript using the form above can email the manuscript department at submit@globaljournals.org or get in touch with chiefeditor@globaljournals.org if they wish to send the abstract before submission.

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Authors must ensure the information provided during the submission of a paper is authentic. Please go through the following checklist before submitting:

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3. Ensure corresponding author's email address and postal address are accurate and reachable.
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Unless specified in the notification, the Editorial Board's decision on publication of the paper is final and cannot be appealed before making the major change in the manuscript.

Acknowledgments

Contributors to the research other than authors credited should be mentioned in Acknowledgments. The source of funding for the research can be included. Suppliers of resources may be mentioned along with their addresses.

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Preparing your Manuscript

Authors can submit papers and articles in an acceptable file format: MS Word (doc, docx), LaTeX (.tex, .zip or .rar including all of your files), Adobe PDF (.pdf), rich text format (.rtf), simple text document (.txt), Open Document Text (.odt), and Apple Pages (.pages). Our professional layout editors will format the entire paper according to our official guidelines. This is one of the highlights of publishing with Global Journals—authors should not be concerned about the formatting of their paper. Global Journals accepts articles and manuscripts in every major language, be it Spanish, Chinese, Japanese, Portuguese, Russian, French, German, Dutch, Italian, Greek, or any other national language, but the title, subtitle, and abstract should be in English. This will facilitate indexing and the pre-peer review process.

The following is the official style and template developed for publication of a research paper. Authors are not required to follow this style during the submission of the paper. It is just for reference purposes.

Manuscript Style Instruction (Optional)

- Microsoft Word Document Setting Instructions.
- Font type of all text should be Swis721 Lt BT.
- Page size: 8.27" x 11'", left margin: 0.65, right margin: 0.65, bottom margin: 0.75.
- Paper title should be in one column of font size 24.
- Author name in font size of 11 in one column.
- Abstract: font size 9 with the word "Abstract" in bold italics.
- Main text: font size 10 with two justified columns.
- Two columns with equal column width of 3.38 and spacing of 0.2.
- First character must be three lines drop-capped.
- The paragraph before spacing of 1 pt and after of 0 pt.
- Line spacing of 1 pt.
- Large images must be in one column.
- The names of first main headings (Heading 1) must be in Roman font, capital letters, and font size of 10.
- The names of second main headings (Heading 2) must not include numbers and must be in italics with a font size of 10.

Structure and Format of Manuscript

The recommended size of an original research paper is under 15,000 words and review papers under 7,000 words. Research articles should be less than 10,000 words. Research papers are usually longer than review papers. Review papers are reports of significant research (typically less than 7,000 words, including tables, figures, and references)

A research paper must include:

a) A title which should be relevant to the theme of the paper.
b) A summary, known as an abstract (less than 150 words), containing the major results and conclusions.
c) Up to 10 keywords that precisely identify the paper's subject, purpose, and focus.
d) An introduction, giving fundamental background objectives.
e) Resources and techniques with sufficient complete experimental details (wherever possible by reference) to permit repetition, sources of information must be given, and numerical methods must be specified by reference.
f) Results which should be presented concisely by well-designed tables and figures.
g) Suitable statistical data should also be given.
h) All data must have been gathered with attention to numerical detail in the planning stage.

Design has been recognized to be essential to experiments for a considerable time, and the editor has decided that any paper that appears not to have adequate numerical treatments of the data will be returned unrefereed.

i) Discussion should cover implications and consequences and not just recapitulate the results; conclusions should also be summarized.
j) There should be brief acknowledgments.
k) There ought to be references in the conventional format. Global Journals recommends APA format.

Authors should carefully consider the preparation of papers to ensure that they communicate effectively. Papers are much more likely to be accepted if they are carefully designed and laid out, contain few or no errors, are summarizing, and follow instructions. They will also be published with much fewer delays than those that require much technical and editorial correction.

The Editorial Board reserves the right to make literary corrections and suggestions to improve brevity.

Format Structure

It is necessary that authors take care in submitting a manuscript that is written in simple language and adheres to published guidelines.

All manuscripts submitted to Global Journals should include:

Title

The title page must carry an informative title that reflects the content, a running title (less than 45 characters together with spaces), names of the authors and co-authors, and the place(s) where the work was carried out.

Author details

The full postal address of any related author(s) must be specified.

Abstract

The abstract is the foundation of the research paper. It should be clear and concise and must contain the objective of the paper and inferences drawn. It is advised to not include big mathematical equations or complicated jargon.

Many researchers searching for information online will use search engines such as Google, Yahoo or others. By optimizing your paper for search engines, you will amplify the chance of someone finding it. In turn, this will make it more likely to be viewed and cited in further works. Global Journals has compiled these guidelines to facilitate you to maximize the web-friendliness of the most public part of your paper.

Keywords

A major lynchpin of research work for the writing of research papers is the keyword search, which one will employ to find both library and internet resources. Up to eleven keywords or very brief phrases have to be given to help data retrieval, mining, and indexing.

One must be persistent and creative in using keywords. An effective keyword search requires a strategy: planning of a list of possible keywords and phrases to try.

Choice of the main keywords is the first tool of writing a research paper. Research paper writing is an art. Keyword search should be as strategic as possible.

One should start brainstorming lists of potential keywords before even beginning searching. Think about the most important concepts related to research work. Ask, “What words would a source have to include to be truly valuable in a research paper?” Then consider synonyms for the important words.

It may take the discovery of only one important paper to steer in the right keyword direction because, in most databases, the keywords under which a research paper is abstracted are listed with the paper.

Numerical Methods

Numerical methods used should be transparent and, where appropriate, supported by references.

Abbreviations

Authors must list all the abbreviations used in the paper at the end of the paper or in a separate table before using them.

Formulas and equations

Authors are advised to submit any mathematical equation using either MathJax, KaTeX, or LaTeX, or in a very high-quality image.

Tables, Figures, and Figure Legends

Tables: Tables should be cautiously designed, uncrowned, and include only essential data. Each must have an Arabic number, e.g., Table 4, a self-explanatory caption, and be on a separate sheet. Authors must submit tables in an editable format and not as images. References to these tables (if any) must be mentioned accurately.

Figures

Figures are supposed to be submitted as separate files. Always include a citation in the text for each figure using Arabic numbers, e.g., Fig. 4. Artwork must be submitted online in vector electronic form or by emailing it.

Preparation of Eletronic Figures for Publication

Although low-quality images are sufficient for review purposes, print publication requires high-quality images to prevent the final product being blurred or fuzzy. Submit (possibly by e-mail) EPS (line art) or TIFF (halftone/ photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Avoid using pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings). Please give the data for figures in black and white or submit a Color Work Agreement form. EPS files must be saved with fonts embedded (and with a TIFF preview, if possible).

For scanned images, the scanning resolution at final image size ought to be as follows to ensure good reproduction: line art: >650 dpi; halftones (including gel photographs): >350 dpi; figures containing both halftone and line images: >650 dpi.

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Tips for writing a good quality Medical Research Paper

1. Choosing the topic: In most cases, the topic is selected by the interests of the author, but it can also be suggested by the guides. You can have several topics, and then judge which you are most comfortable with. This may be done by asking several questions of yourself, like "Will I be able to carry out a search in this area? Will I find all necessary resources to accomplish the search? Will I be able to find all information in this field area?" If the answer to this type of question is "yes," then you ought to choose that topic. In most cases, you may have to conduct surveys and visit several places. Also, you might have to do a lot of work to find all the rises and falls of the various data on that subject. Sometimes, detailed information plays a vital role, instead of short information. Evaluators are human: The first thing to remember is that evaluators are also human beings. They are not only meant for rejecting a paper. They are here to evaluate your paper. So present your best aspect.

2. Think like evaluators: If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research paper, and you will automatically have your answer. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

3. Ask your guides: If you are having any difficulty with your research, then do not hesitate to share your difficulty with your guide (if you have one). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work, then ask your supervisor to help you with an alternative. He or she might also provide you with a list of essential readings.

4. Use of computer is recommended: As you are doing research in the field of medical research then this point is quite obvious. Use right software: Always use good quality software packages. If you are not capable of judging good software, then you can lose the quality of your paper unknowingly. There are various programs available to help you which you can get through the internet.

5. Use the internet for help: An excellent start for your paper is using Google. It is a wondrous search engine, where you can have your doubts resolved. You may also read some answers for the frequent question of how to write your research paper or find a model research paper. You can download books from the internet. If you have all the required books, place importance on reading, selecting, and analyzing the specified information. Then sketch out your research paper. Use big pictures: You may use encyclopedias like Wikipedia to get pictures with the best resolution. At Global Journals, you should strictly follow here.

6. Bookmarks are useful: When you read any book or magazine, you generally use bookmarks, right? It is a good habit which helps to not lose your continuity. You should always use bookmarks while searching on the internet also, which will make your search easier.

7. Revise what you wrote: When you write anything, always read it, summarize it, and then finalize it.

8. Make every effort: Make every effort to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in the introduction—what is the need for a particular research paper. Polish your work with good writing skills and always give an evaluator what he wants. Make backups: When you are going to do any important thing like making a research paper, you should always have backup copies of it either on your computer or on paper. This protects you from losing any portion of your important data.

9. Produce good diagrams of your own: Always try to include good charts or diagrams in your paper to improve quality. Using several unnecessary diagrams will degrade the quality of your paper by creating a hodgepodge. So always try to include diagrams which were made by you to improve the readability of your paper. Use of direct quotes: When you do research relevant to literature, history, or current affairs, then use of quotes becomes essential, but if the study is relevant to science, use of quotes is not preferable.

10. Use proper verb tense: Use proper verb tenses in your paper. Use past tense to present those events that have happened. Use present tense to indicate events that are going on. Use future tense to indicate events that will happen in the future. Use of wrong tenses will confuse the evaluator. Avoid sentences that are incomplete.

11. Pick a good study spot: Always try to pick a spot for your research which is quiet. Not every spot is good for studying.

12. Know what you know: Always try to know what you know by making objectives, otherwise you will be confused and unable to achieve your target.

13. Use good grammar: Always use good grammar and words that will have a positive impact on the evaluator; use of good vocabulary does not mean using tough words which the evaluator has to find in a dictionary. Do not fragment sentences. Eliminate one-word sentences. Do not ever use a big word when a smaller one would suffice.

Verbs have to be in agreement with their subjects. In a research paper, do not start sentences with conjunctions or finish them with prepositions. When writing formally, it is advisable to never split an infinitive because someone will (wrongly) complain. Avoid clichés like a disease. Always shun irritating alliteration. Use language which is simple and straightforward. Put together a neat summary.

14. Arrangement of information: Each section of the main body should start with an opening sentence, and there should be a changeover at the end of the section. Give only valid and powerful arguments for your topic. You may also maintain your arguments with records.

15. Never start at the last minute: Always allow enough time for research work. Leaving everything to the last minute will degrade your paper and spoil your work.

16. Multitasking in research is not good: Doing several things at the same time is a bad habit in the case of research activity. Research is an area where everything has a particular time slot. Divide your research work into parts, and do a particular part in a particular time slot.

17. Never copy others' work: Never copy others' work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not taking care of your health, then all your efforts will have been in vain. For quality research, take proper rest and food.

18. Go to seminars: Attend seminars if the topic is relevant to your research area. Utilize all your resources.

19. Refresh your mind after intervals: Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.

20. Think technically: Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

21. Adding unnecessary information: Do not add unnecessary information like "I have used MS Excel to draw graphs." Irrelevant and inappropriate material is superfluous. Foreign terminology and phrases are not apropos. One should never take a broad view. Analogy is like feathers on a snake. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Never oversimplify: When adding material to your research paper, never go for oversimplification; this will definitely irritate the evaluator. Be specific. Never use rhythmic redundancies. Contractions shouldn't be used in a research paper. Comparisons are as terrible as clichés. Give up ampersands, abbreviations, and so on. Remove commas that are not necessary. Parenthetical words should be between brackets or commas. Understatement is always the best way to put forward earth-shaking thoughts. Give a detailed literary review.

22. Report concluded results: Use concluded results. From raw data, filter the results, and then conclude your studies based on measurements and observations taken. An appropriate number of decimal places should be used. Parenthetical remarks are prohibited here. Proofread carefully at the final stage. At the end, give an outline to your arguments. Spot perspectives of further study of the subject. Justify your conclusion at the bottom sufficiently, which will probably include examples.

23. Upon conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium though which your research is going to be in print for the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects of your research.

Informal Guidelines of Research Paper Writing

Key points to remember:

- Submit all work in its final form.
- Write your paper in the form which is presented in the guidelines using the template.
- Please note the criteria peer reviewers will use for grading the final paper.

Final points:

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

The introduction: This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

The discussion section:

This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to prior workings.

Writing a research paper is not an easy job, no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record-keeping are the only means to make straightforward progression.

General style:

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

To make a paper clear: Adhere to recommended page limits.

Mistakes to avoid:

- Insertion of a title at the foot of a page with subsequent text on the next page.
- Separating a table, chart, or figure—confine each to a single page.
- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

Title page:

Choose a revealing title. It should be short and include the name(s) and address(es) of all authors. It should not have acronyms or abbreviations or exceed two printed lines.

Abstract: This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

An abstract is a brief, distinct paragraph summary of finished work or work in development. In a minute or less, a reviewer can be taught the foundation behind the study, common approaches to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study with the subsequent elements in any summary. Try to limit the initial two items to no more than one line each.

Reason for writing the article—theory, overall issue, purpose.

- Fundamental goal.
- To-the-point depiction of the research.
- Consequences, including definite statistics—if the consequences are quantitative in nature, account for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

Approach:

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else.

Introduction:

The introduction should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.

The following approach can create a valuable beginning:

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study's tentative purpose and how it meets the declared objectives.

Approach:

Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done. Sort out your thoughts; manufacture one key point for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory specifically—do not take a broad view.

As always, give awareness to spelling, simplicity, and correctness of sentences and phrases.

Procedures (methods and materials):

This part is supposed to be the easiest to carve if you have good skills. A soundly written procedures segment allows a capable scientist to replicate your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order, but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt to give the least amount of information that would permit another capable scientist to replicate your outcome, but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section.

When a technique is used that has been well-described in another section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show all particular resources and broad procedures so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step-by-step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

Materials may be reported in part of a section or else they may be recognized along with your measures.

Methods:

- Report the method and not the particulars of each process that engaged the same methodology.
- Describe the method entirely.
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures.
- Simplify—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that's all.

Approach:

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and every other part of the paper—avoid familiar lists, and use full sentences.

What to keep away from:

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings—save it for the argument.
- Leave out information that is immaterial to a third party.

Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

Content:

- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or manuscript.

What to stay away from:

- Do not discuss or infer your outcome, report surrounding information, or try to explain anything.
- Do not include raw data or intermediate calculations in a research manuscript.
- Do not present similar data more than once.
- A manuscript should complement any figures or tables, not duplicate information.
- Never confuse figures with tables—there is a difference.

Approach:

As always, use past tense when you submit your results, and put the whole thing in a reasonable order.

Put figures and tables, appropriately numbered, in order at the end of the report.

If you desire, you may place your figures and tables properly within the text of your results section.

Figures and tables:

If you put figures and tables at the end of some details, make certain that they are visibly distinguished from any attached appendix materials, such as raw facts. Whatever the position, each table must be titled, numbered one after the other, and include a heading. All figures and tables must be divided from the text.

Discussion:

The discussion is expected to be the trickiest segment to write. A lot of papers submitted to the journal are discarded based on problems with the discussion. There is no rule for how long an argument should be.

Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully described.

Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact, you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved the prospect, and let it drop at that. Make a decision as to whether each premise is supported or discarded or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."

Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work.

- You may propose future guidelines, such as how an experiment might be personalized to accomplish a new idea.
- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of research will not counter an overall question, so maintain the large picture in mind. Where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

When you refer to information, differentiate data generated by your own studies from other available information. Present work done by specific persons (including you) in past tense.

Describe generally acknowledged facts and main beliefs in present tense.

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Introduction	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
Methods and Procedures	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
Result	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
Discussion	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

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