

Original Article

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Interpersonal Education in Medical Students: A Bibliometric Analysis From 2014 to 2024

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ABSTRACT

Introduction: The urgency to set a new strategy at teaching and learning that improve healthcare quality based on collaborative work among different professionals, interprofessional education becomes an emerging topic, being considered an important approach in health curriculum. The aim of the study is to investigate the research hotspots and theme trends in Interprofessional education in medical student through bibliometric analysis.

Methods: Relevant articles on Interprofessional education in medical student published between 2014 and 2024 were retrieved from SCOPUS. The VOSviewer was used to extract and quantitatively analyze the publications data in three dimensions such as network, overlay and density visualization.

Result: A total a total of 1702 publications which we limit to those published within the year of 2014-2024 and 512 publications met all of the requirements. Afterwards, co- occurrence analysis was conducted and a network map was also developed using VOSviewer tool. The results showed the trend based on the annual number of publications; most contributing authors; most contributing countries; most published journals; keyword analyses; gaps and potential future study topics.

Conclusion: This study demonstrated the publication trends regarding the implementation of interprofessional education in medical student over the past 10 years. The analysis results using VOSviewer showed that there are still some topics about interprofessional education that need to be explored in the future.

Keywords: Interprofessional education; medical student; Bibliometric



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Introduction

Continuous improvement in technology and treatment modalities makes the health care sector a complex environment, and all healthcare professionals need to keep up with new advancements to ensure positive health outcomes for individuals and families. To achieve this objective, all health professionals, regardless of their discipline, need to practice collaboratively. Various models of interprofessional education (IPE) exist, and academics must include these models and frameworks in undergraduate education to prepare students for interprofessional collaborative practice in the health care environment.¹ Currently, various accrediting bodies, standards, and guidelines require health professionals to promote IPE in undergraduate education. IPE is promoted in pharmacy, dentistry, medicine, nursing, and other allied health professions.² The Center for Advancement of IPE (CAIPE) defines IPE as “a teaching and learning process that fosters collaborative work and improves quality of care between two or more professions. IPE occurs when students learn with, from, and about one another”.³

This definition has also been adopted by the Canadian Interprofessional Health Collaborative (CIHC) and seems to be the most widely accepted definition.⁴ The CIHC adds that IPE occurs when health care professionals learn collaboratively within and across disciplines to acquire knowledge, skills, and values needed for working in teams. Considering this context and aiming at teaching and learning strategies that improve healthcare quality based on collaborative work among different professionals, interprofessional education becomes an emerging topic, being considered an important pedagogical approach in health curricula. Today, we can see that ASEAN's countries are trying to apply the concept of IPE in their medical and health science education. Even a country like Singapore already had a well maintained IPE's program and creating a sustainable IPE's platform for Asian university.⁵ Narrowing the area into Indonesia, several journals were reporting the implementation of IPE in medical and health science curricula, assessing the outcomes and deliver some suggestion for that.

We undertook a bibliometric analysis of Interprofessional Education in Medical Student. The aims of this study are to review interprofessional education literature by providing a thorough bibliometric analysis to investigate the trend based on the annual number of publications; most contributing authors; most contributing countries; most published journals; keyword analyses; gaps and potential future study topics; Additionally, this study aims to provide a comprehensive description of the current state of knowledge in the field of interprofessional education.

Methods

This is a bibliometric study on the topic. The implementation of Interprofessional Education in Medical Student. The bibliometric method is a useful approach to identify the emerging trends and abrupt changes in a research field. It contains a series of quantitative methods to study academic literature and develop the distribution patterns or internal relationship of a specific topic, field, institute, or country.⁶

SCOPUS is one of the most authoritative data bases used in bibliometric studies. Scopus is among the available databases with the broadest worldwide coverage of publications including journals, books, and conferences, as well as articles.⁷ Scopus is also user-friendly and supports multiple software packages for obtaining bibliometric information (authors, titles, publication dates, references, abstracts, institutions, and countries).⁸

SCOPUS is more effective to analyze the overall development of a research field. Based on this, we choose SCOPUS to conduct our research. The main purpose of this study is to investigate the emerging trends of the search of interprofessional education in medical education. The data used in the present study are downloaded from SCOPUS on 15 May 2024 using keyword "Interprofessional education" AND "medical education" OR "medical student".

The initial search of keyword showed a total of 1702 publications which we limit to those published within the year of 2014-2024, published in subject area of medicine, document type of article, keyword limit of medical education and medical student and publications published using English language and 512 publications met all of the requirements. Afterwards, co-occurrence analysis was conducted and a network map was also developed using VOSviewer tool. VOSviewer is chosen to perform the results of the analysis because of its outstanding analytics and visualization capabilities as well as its free access.

In this study, the VOSviewer was employed to visually analyze co-occurrence patterns, with circles representing the breakdown of countries and author keywords. The distance between two circles indicated the strength of the relationship between terms, with greater distance suggesting a weaker relationship. Various colors in the visualization denoted different term clusters, while the size of the circles was proportional with the frequency of terms. Additionally, the line thickness corresponded to the strength of the relationship between terms. The higher the diameter of the circle, the greater the frequency of the terms. The flow of the data search strategy as well as its analysis are depicted in FIGURE 1

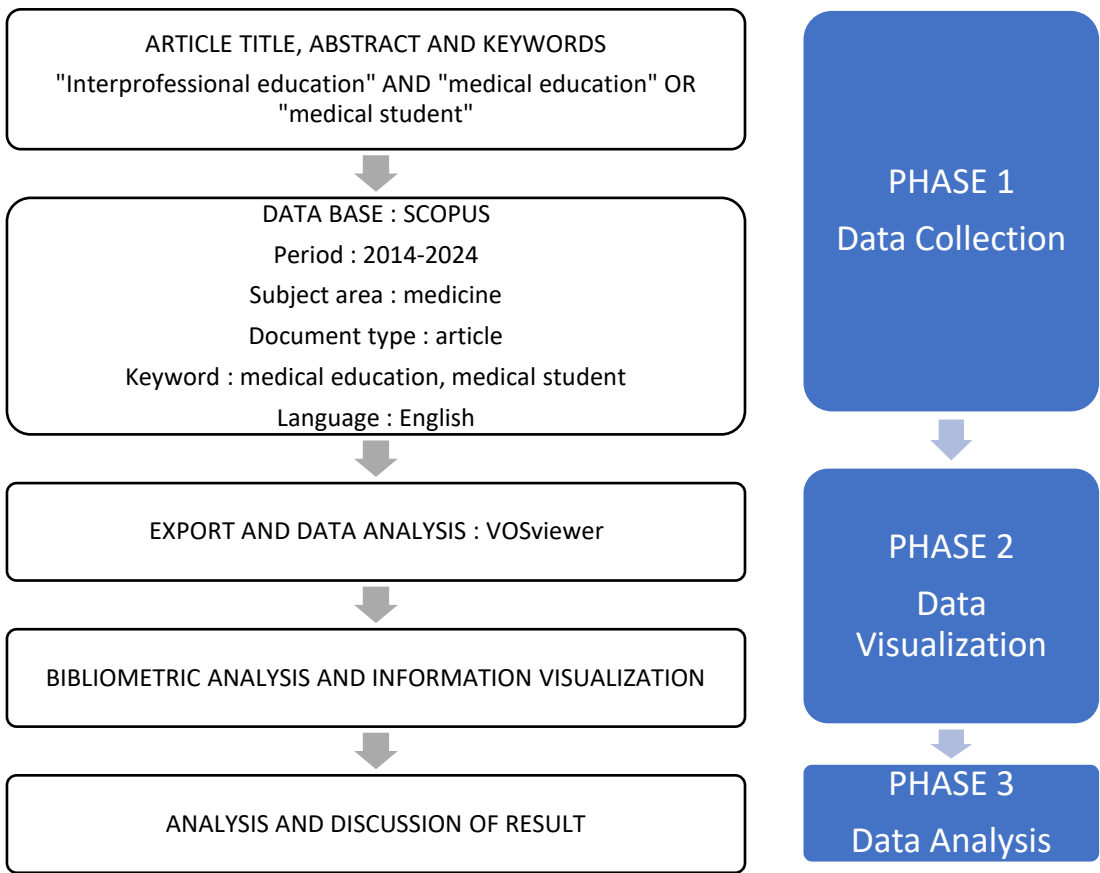


Figure 1. The methodology phases on constructing bibliometric analysis

Result
Publication Trends

The publication trends showed in Figure 2. A decline was observed from 2015 and 2018; then an upward trend was observed from 2018 to 2020; this period may have been associated with increased awareness, research funding, and the global issues of interprofessional education. During 2020 and 2021 there is a slight decline observed that may have been associated with COVID-19 pandemic then stagnant result observed in 2022 and 2023. At this time this study was conducted, 2024 was still in progress so the number of publications for that year may have decreased from 2023.

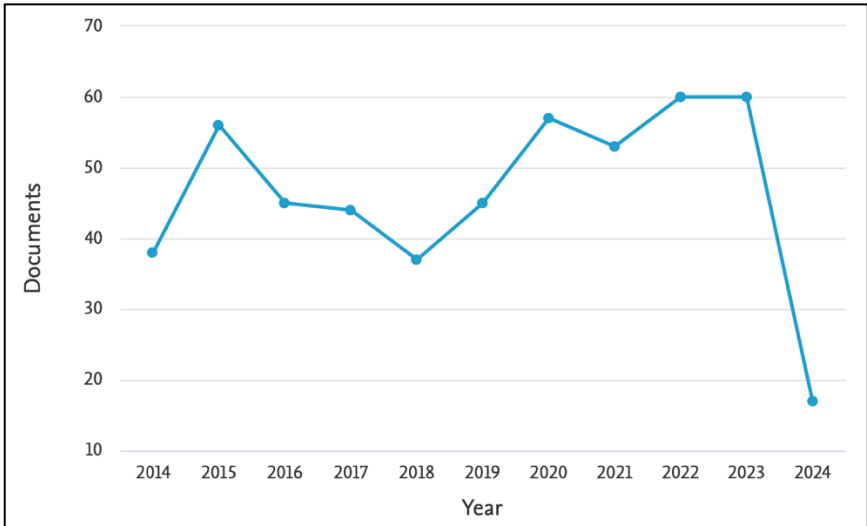


Figure 2. Interprofessional Education research trends on a world-wide scale (2014-2024)

Based on the most contributing authors, Mahler C from Universitätsklinikum Tübingen, Abteilung Pflegewissenschaft, Tübingen, Germany is the author with the most contributions with 6 articles and a total of 144 citations. His most influential article is about “Position statement GMA committee – “interprofessional education for the health care professions” in 2015 with 83 citations, while his current publication is “Interprofessional socialization and collaboration on an interprofessional training ward – a reconstructive analysis” in 2022 with 3 citations. **Figure 3** shows the top ten contributors of articles published in SCOPUS regarding Interprofessional Education in Medical Student.



Figure 3. Authors’ production on Interprofessional education research

As shown in Figure 4, the top 5 journals that published the most articles in the field of Interprofessional education in medical student over the past 10 years. Journal of interprofessional Care published 120 articles, followed by Mededportal the Journal of Teaching and Learning Resources published 26 articles then Anatomical Sciences Education published 12 articles.

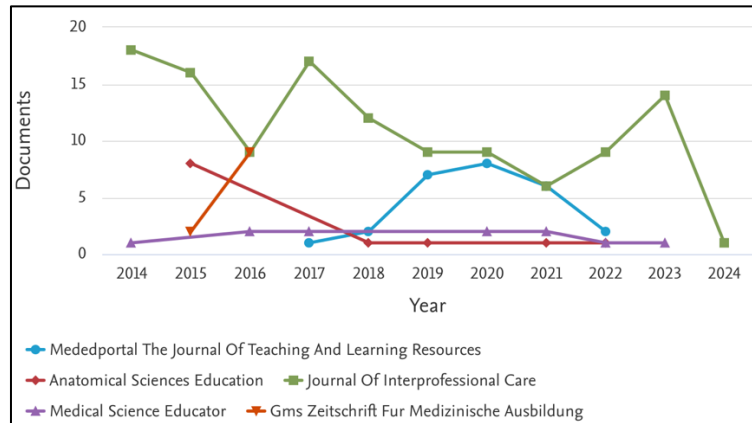


Figure 4. Journals published articles in the field of Interprofessional education

The top ten countries based on publication number in the field of Interprofessional Education in Medical Student are presented in Figure 5. United States published the most documents concerning Interprofessional education, with 257 publications (50,19%), followed by United Kingdom with 53 (10,35%), and Italy in the 10th positions with 6 publications (1,1%).

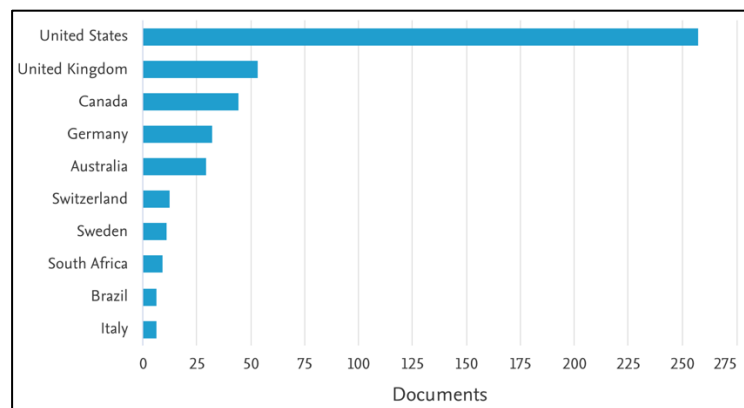


Figure 5. Countries based on publication number in the field of Interprofessional Education

Based on the bibliographic information, we retrieved the results using VOSviewer and set the minimum keyword frequency at 5. We collected 1170 keywords and 55 meet the threshold. Table 1 shows seven clusters and their linkages among examined areas. Each cluster consisted of numerous keywords including the most frequent keywords and the number of occurrences from the bibliometric analysis with VOSviewer. In figure 6, showed the network visualization where VOSviewer's default labelling and depiction of Interprofessional Education in Medical Student study topic-related objects (keywords) are circles; the size of the label and the circle of an item is determined by the weight of the item. The higher the weight of an item, the larger the label and the circle of the item. The color of an item is determined by the cluster to which the item belongs. Lines between items represent links. The distance between two journals in the visualization approximately indicates the relatedness of the journals in terms of co-citation links. In general, the closer two journals are located to each other, the stronger their relatedness. The strongest co-citation links between journals are also represented by lines.

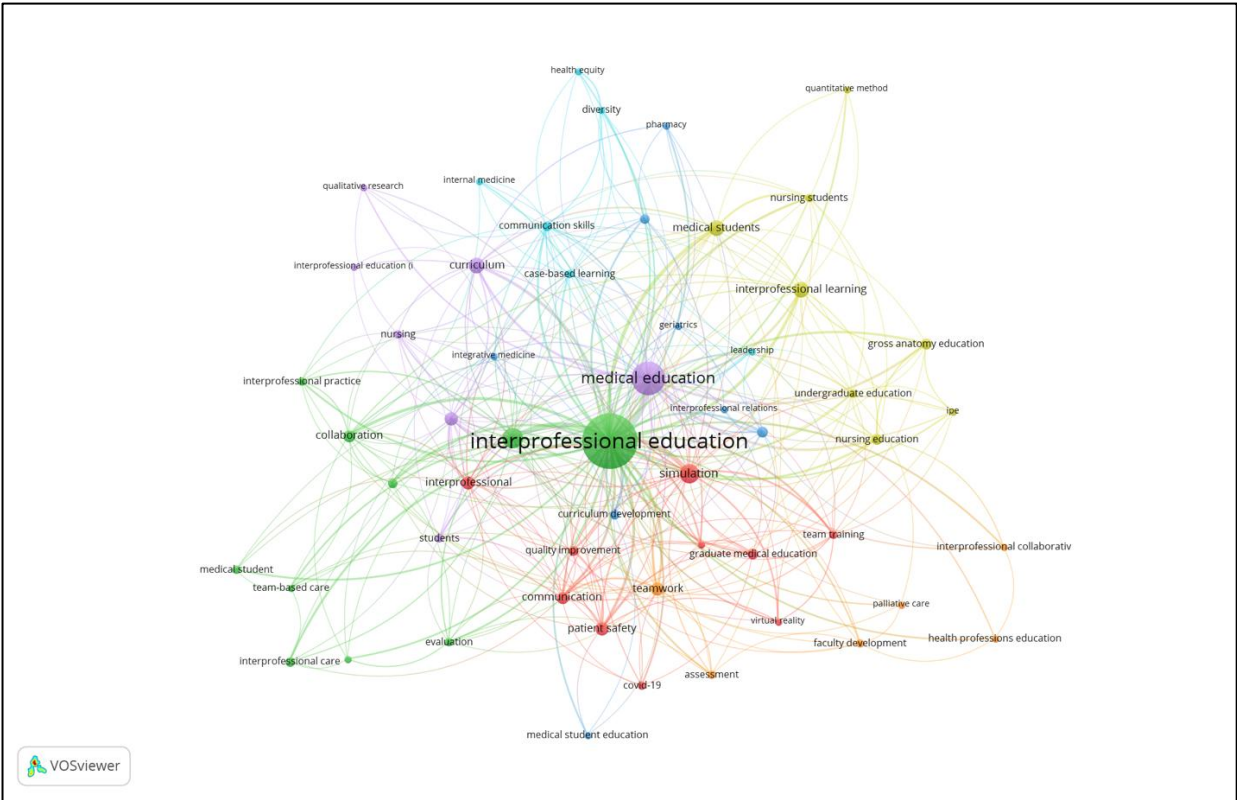


Figure 6. Network visualization of Interprofessional education-related publications

Figure 7 (overlay visualizations) depicts a research topic by year from 2014-2024 and provides comprehensive view of research topics evolving over time. This historical perspective allows us to trace the field’s changing research emphasis and trends, reflecting the evolution of knowledge and scientific priorities. The overlay visualization is identical to the network visualization except that items are colored differently.

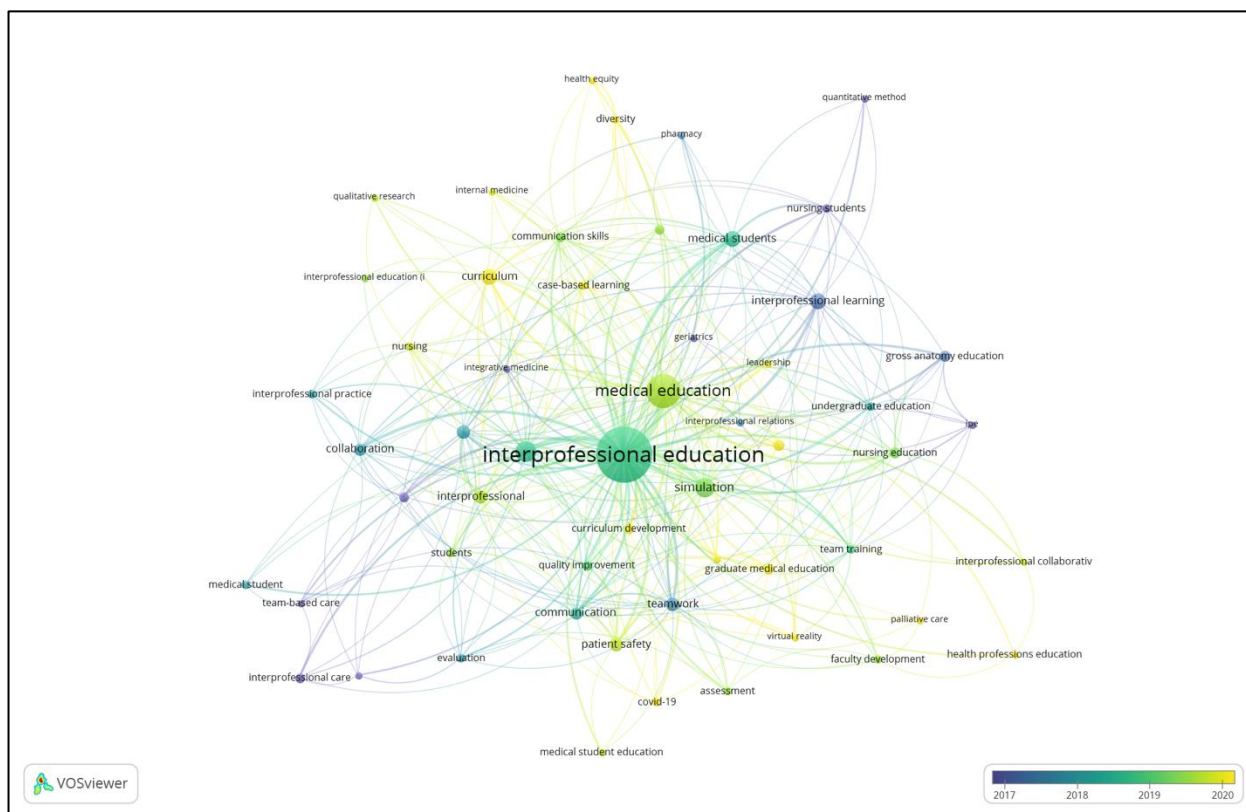


Figure 7. Overlay visualization of Interprofessional education-related publications

In figure 8, illustrates density visualization, which demonstrates the breadth of Interprofessional Education in medical students' study. In the item density visualization, items are represented by their label in a similar way as in the network visualization and the overlay visualization. Each point in the item density visualization has a color that indicates the density of items at that point. By default, colors range from blue to green to yellow. The larger the number of items in the neighborhood of a point and the higher the weights of the neighboring items, the closer the color of the point is too yellow. The other way around, the smaller the number of items in the neighborhood of a point and the lower the weights of the neighboring items, the closer the color of the point is too blue.

Thus, the keyword with the lowest frequency, represented by a diffuse hue, indicates that the research topic is yet underdeveloped and requires additional exploration in the future studies. In this study, the underdeveloped topics were health equity, qualitative research, quantitative, diversity, pharmacy. These underexplored areas give opportunity to the new researchers to contribute to the development of interprofessional education in medical student.

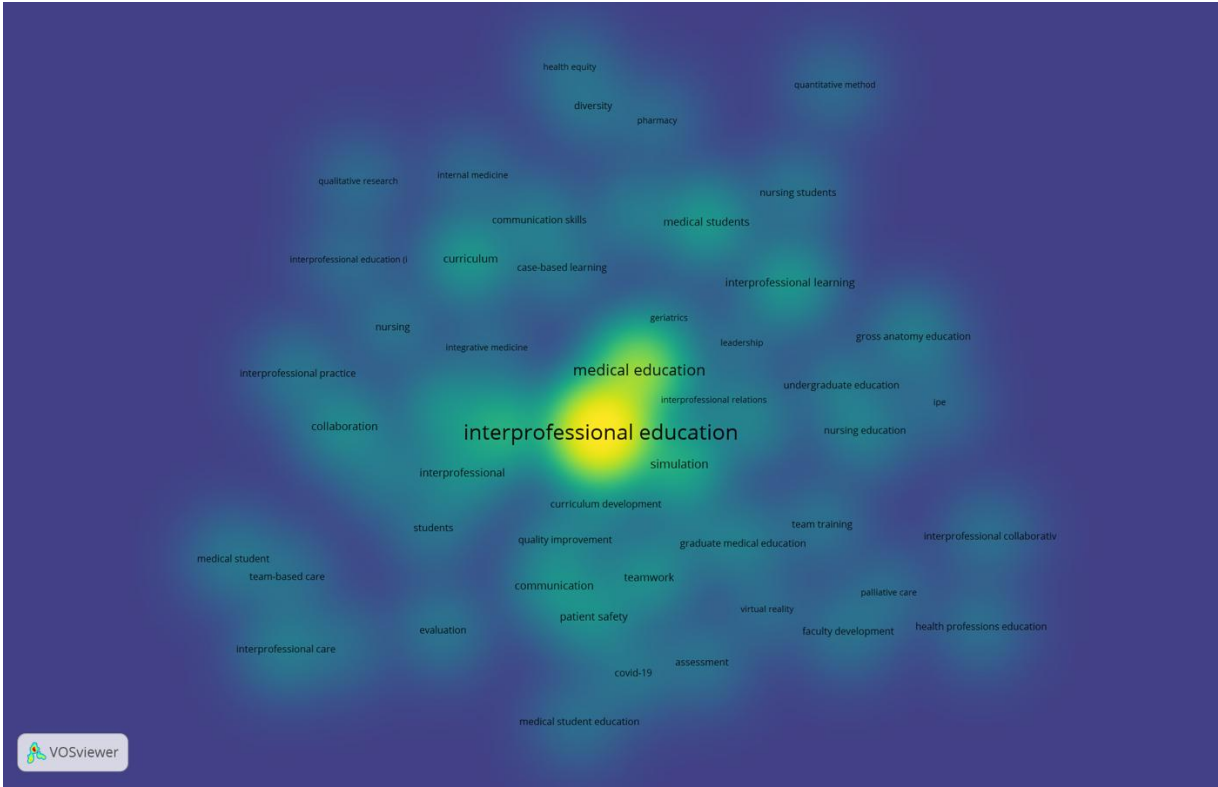


Figure 8. Density visualization of Interprofessional education-related publications

Table 1. The result of cluster analysis on Interprofessional education publications

Cluster	More frequent keywords	Keywords (Number of Occurrence)
1 st cluster (10 items)	Simulation (38), interprofessional (17), patient safety (17)	Communication (16), graduate medical education (11), quality improvement (10), covid-19 (8), team training (7), interprofessional communication (6), virtual reality (5)
2 nd cluster (10 items)	interprofessional education (297), interprofessional collaboration (41), Collaboration (16)	interprofessional care (10) mixed methods (9) evaluation (8) interprofessional practice (8) medical student (8) team-based care (6) interprofessional evaluation (5)
3 rd cluster (8 items)	Undergraduate medical education (12) primary care (10) curriculum development (9)	medical student education (6), geriatrics (5) integrative medicine (5) interprofessional relations (5) pharmacy (5)
4 th cluster (8 items)	medical students (24) interprofessional (23) gross anatomy education (11)	nursing education (11) nursing education (8) undergraduate education(8) IPE(5) quantitative method (5)
5 th cluster (7 items)	medical education (109) curriculum (23) education (19)	Nursing (7) Students (7) Interprofessional education (ipe) (5) qualitative research (5)

6th cluster (6 items)	communication skills (10) case-based learning (8) diversity (6)	health equity (5) internal medicine (5) leadership (5)
7th cluster (6 items)	Teamwork (18) Assement (7) faculty development (7)	health professions education interprofessional (6) collaborative practice (6) palliative care (5)

Discussion

This study was primarily aimed to explore the current status, research hotspots, and theme trends of interprofessional education in medical student from 2014 to 2024. A total 512 publications originating from SCOPUS were analyzed in this study. An increasing number and trends of publications were observed on this topic, especially from 2018 to 2020. The VOSviewer analysis yielded 7 clusters. These might be the candidate topics for future in-depth research.

The first cluster with “simulation”, “interprofessional” and “patient safety” as the most frequent keywords. In 2013, WHO guidelines highlighted the necessity to employ IPE and simulation together in professional healthcare education to address issues related to collaboration and communication, improve patient safety and promote positive patient outcomes.⁹

Recent studies have revealed an increasing trend in the use of interprofessional simulation in different health care undergraduate students and professional staff.^{10, 11, 12}

A recent systematic review and meta-analysis have shown that interprofessional simulation is an effective learning method to improve the collaborative competencies of the participants.¹³ However, there are still measurable gaps in this field. The lack of randomized clinical trial studies, inadequate sample sizes, and varied content and structural scales may yield a high risk of bias and low-quality evidence.

The second cluster focuses on collaboration in interprofessional education. Delivery of quality health care is likewise a function of effective teamwork among individuals providing care. Respect, understanding, and collaboration across professions are key components to successful health care teams. In order for health care organizations to uphold a collaborative environment, understanding the attitudes and collaborative competencies of health care professionals is a necessary first step. Additionally, understanding characteristics related to the type and amount of IPE health care professionals complete is imperative in order to design effective IPE experiences.¹⁴ The third cluster mostly talked about undergraduate medical education. In most parts of the world, educational activities for every profession at the undergraduate level are performed independently from one another (i.e., each profession plans and conducts its own teaching). As a result, graduates have limited knowledge about other professions, limited communication, collaboration, and teamwork skills and must wait until they enter an actual work environment before they can interact with other professions.¹⁵ Therefore Interprofessional education need to be implemented in undergraduate curricula.

This bibliometric analysis' findings have also shown that there are still some topics about interprofessional education that need to be explored in the future such as health equity, the need of qualitative or quantitative study to measure the impact of interprofessional education, and also research focuses on pharmacy.

Conclusion

This study demonstrated the publications trends and listed the most influential countries, journals and authors regarding the implementation of interprofessional education in medical student over the past 10 years. Using the VOSviewer analyses, we identified the network, overlay and density visualization of the publications found on SCOPUS. The result showed that there are still some topics about interprofessional education that need to be explored in the future. research question, and not expressed in statistical sentences. Use terms with substantive scientific meaning and avoid statistical/methodological technical terms.

Conflicts of Interest

There is no conflict of interest.

Funding sources

There is no funding source

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References

1. Olenick M, Allen LR, Smego RA Jr. Interprofessional education: a concept analysis. *Adv Med Educ Pract* 2010 Nov; 1:75-84
2. Shakhman L.M., Omari O.A., et al. Interprofessional education and collaboration: strategies for implementation. *Oman Medical Journal* [2020], Vol. 35, No. 3: e160
3. Centre for the Advancement of Interprofessional Education (CAIPE). Available from: <http://www.caipe.org.uk/about-us/defining-ipe/?keywords=definition>. Accessed 2009 Aug 18.
4. Canadian Interprofessional Health Collaborative (CIHC). Available from: <http://www.cihc.ca/>. Accessed 2008 Nov 8.
5. J.L. Jacobs, et al. "Building a successful platform for interprofessional education for health professions in an Asian university," *Education for Health*, vol. 26, 2013
6. X. Zhao, S. Wang, X. Wang, Characteristics and trends of research on new energy vehicle reliability based on the web of science, *Sustainability* 10 (2018) 3560, DOI: <https://doi.org/10.3390/su10103560>.
7. J. Baas, M. Schotten, A. Plume, G. Côté, R. Karimi, Scopus as a curated, high-quality bibliometric data source for academic research in quantitative science studies, *Quantitative Science Studies* 1 (2020) 377–386, https://doi.org/10.1162/qss_a_00019.
8. H. Sikandar, Y. Vacondam, N. Khan, M. I. Qureshi, A. Ullah, Scientific mapping of industry 4.0 research: a bibliometric analysis, *International Journal of Interactive Mobile Technologies (IJIM)* 15 (2021) 129, <https://doi.org/10.3991/ijim.v15i18.25535>.
9. WHO, 2013. Transforming and Scaling up Health Professionals' Education and Training: World Health Organization Guidelines 2013. World Health Organization.
10. Gellis, Z.D., Eunhae, K., Diane, H., Lora, P., Cathy, P., Ann, F.M., Tara, H., 2018. Evaluation of interprofessional health care team communication simulation in geriatric palliative care. *Gerontol. Geriatr. Educ.* 40, 1–13.
11. Shi, R., Marin-Nevarez, P., Hasty, B., Roman-Micek, T., Hirx, S., Anderson, T., Lau, J.N., 2021. Operating room in situ interprofessional simulation for improving communication and teamwork. *J. Surg. Res.* 260, 237–244. <https://doi.org/10.1016/j.jss.2020.11.051>.
12. Wen, A., Wong, L., Ma, C., Arndt, R., Katz, A.R., Richardson, K., Masaki, K., 2019. An interprofessional team simulation exercise about a complex geriatric patient. *Gerontol. Geriatr. Educ.* 40 (1), 16–29. <https://doi.org/10.1080/02701960.2018.1554568>.
13. Marion-Martins, A.D., Pinho, D.L.M., 2020. Interprofessional simulation effects for healthcare students: a systematic review and meta-analysis. *Nurse Educ. Today* 94, 104568. <https://doi.org/10.1016/j.nedt.2020.104568>.
14. Staduck, J.L. The relationship between interprofessional education and health care professional's attitudes towards teamwork and interprofessional collaborative competencies. *Journal of Interprofessional Education & Practice* Volume 19, June 2020, 100320. DOI: <https://doi.org/10.1016/j.xjep.2020.100320>
15. Aldriwesh, M.G., Alyousif, S.M. & Alharbi, N.S. Undergraduate-level teaching and learning approaches for interprofessional education in the health professions: a systematic review. *BMC Med Educ* 22, 13 (2022). <https://doi.org/10.1186/s12909-021-03073-0>

Review article

Open Access

Regulation of eNOS (Endothelial Nitric Oxide Synthase) in Nephrotic Syndrome Pathophysiology: Literature Review

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ABSTRACT

Introduction: Nephrotic syndrome (NS) is a chronic pediatric kidney disorder marked by proteinuria, edema, and impaired renal function, with eNOS-derived nitric oxide (NO) dysregulation implicated in its pathogenesis.

Methods: This literature review analyzed studies discussing the role of eNOS in the pathogenesis of NS, particularly steroid-sensitive nephrotic syndrome (SSNS) in pediatric patients. Relevant articles were identified from scientific databases using keywords related to nephrotic syndrome, eNOS, nitric oxide, and renal dysfunction. The selected studies included experimental, genetic, and clinical investigations evaluating eNOS expression, NO production, and associated renal outcomes. Data from the included studies were synthesized narratively to identify the relationship between eNOS dysregulation and NS progression.

Results: The reviewed studies demonstrated that eNOS-derived NO is essential for renal vasodilation, sodium excretion, and blood pressure regulation. Reduced eNOS activity and decreased NO availability were associated with proteinuria, sodium retention, edema, and hypertension in NS. Several studies reported that eNOS polymorphisms, including eNOS4a/b VNTR, were linked to lower plasma NO levels and progressive glomerular injury. Experimental models of NS also showed decreased eNOS and neuronal NOS expression, resulting in impaired natriuresis and renal dysfunction.

Conclusion: Dysregulation of the eNOS–NO pathway may contribute to NS through altered sodium handling, vascular tone, and blood pressure regulation. However, evidence is heterogeneous, with urinary NO metabolites, genetic polymorphisms, and tissue eNOS expression showing inconsistent patterns. Further pediatric studies are needed to clarify the relationship between eNOS, NO bioavailability, and clinical outcomes before eNOS-directed therapies can be recommended.

Keywords: Nephrotic syndrome; endothelial Nitric Oxide Synthase; vasodilation; blood pressure; endothelial cell



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Introduction

High salt retention and the development of edema are the features of nephrotic syndrome (NS). Fluid moves from the intravascular compartment to the interstitial space and plasma volume decreases as a result of this condition, which is related to a decrease in plasma albumin levels (plasma oncotic pressure). Decreased intravascular volume is estimated to cause the renal tubules to reabsorb water and salt by activating the renin-angiotensin-aldosterone sequence, increasing sympathetic response, and increase vasopressin, and preventing the synthesis of atrial natriuretic peptide. Due to inherent abnormalities in tubular sodium transport and renal hemodynamics that are incompatible with hypoalbuminemia and hypovolemia, this concept is currently under the discussion.^{1,2}

Humans and mice with congenital analbuminaemia typically have an absence of edema. Additionally, patients with nephrotic syndrome typically have normal or elevated plasma volume. Furthermore, intravascular volume depletion in nephrotic syndrome has not consistently been demonstrated by reassuring functional plasma indicators, such as hematocrit or plasma concentrations of renin, vasopressin, norepinephrine, aldosterone, and atrial natriuretic peptide. In fact, patients with nephrotic syndrome typically have normal levels of atrial natriuretic peptide, vasopressin, and norepinephrine, but decreased levels of renin activity and aldosterone. Another study showed that natriuresis triggers an increase in levels of serum albumin in individuals with nephrotic that establish remission with steroid, and notably, aldosterone and plasma renin activity increase as edema resolves.^{1,2,3}

Nitric oxide (NO) is a messenger molecule that regulates several biological processes and is present in many different places. Nitric oxide is created by the stereospecific oxidation of L-arginine by a group of enzymes known as nitric oxide synthases (NOS). Nitric oxide synthases (NOS) are a class of enzymes that produce nitric oxide through the stereospecific oxidation of L-arginine. NOS has three specific isoforms: NOS I or neuronal NOS (nNOS), NOS II or inducible NOS (iNOS), and NOS III or endothelial NOS (eNOS). Vasodilatory tone, which is sustained by the stimulating release of NO from eNOS-iNOS in systemic and renal arteries, controls blood pressure, tissue perfusion, and renal and vascular system resistance. Furthermore, intrarenal NO regulates as an endogenous diuretic by acting as primary regulator of water and sodium excretion by the renal system. By preventing sodium reabsorption, NO produced in tubular epithelial cells by iNOS stimulates natriuresis. Additionally, NO produced by nNOS in the macula densa reduces afferent arteriolar vasoconstriction associated with tubuloglomerular feedback in response to changes in Na concentration in the lumen, promoting glomerular filtration and Na excretion.^{4,5,6}

eNOS has been the subject of ongoing research, but its specific contribution to nephrotic syndrome remains incompletely defined. Previous studies have reported reduced renal NOS expression in experimental nephrotic syndrome, increased urinary NO metabolites in children with minimal change nephrotic syndrome, and associations between eNOS gene polymorphisms and susceptibility to nephrotic syndrome. However, these findings do not consistently establish whether altered eNOS expression or activity leads to reduced NO

bioavailability and impaired natriuresis, or whether increased urinary NO metabolites represent a compensatory response or increased NO production from other NOS isoforms. Furthermore, the relationship between eNOS-related abnormalities and clinical outcomes such as sodium retention, edema, hypertension, proteinuria, and disease relapse remains uncertain, particularly in children with nephrotic syndrome. Therefore, this review aims to synthesize the available experimental, genetic, and clinical evidence regarding eNOS expression and activity, NO bioavailability and urinary NO metabolites, eNOS genetic polymorphisms, and their associations with the pathophysiology and potential therapeutic implications of nephrotic syndrome.

Nephrotic Syndrome

Protein leaking from the circulation into the urine through damaged glomeruli is the hallmark of NS. This syndrome is defined by proteinuria (≥ 40 mg/m²/hour or urine protein-to-creatinine ratio ≥ 200 mg/mg or 3+ protein on urine test), hypoalbuminemia (< 25 g/L), and edema. The Consensus of Idiopathic Nephrotic Syndrome in Children issued by the Indonesian Pediatric Society (IDAI) explains that the diagnostic criteria for NS are massive proteinuria, hypoalbuminemia, edema, and may be accompanied by hypercholesterolemia.⁷

Congenital SN in children might manifest during their early three months of life, and is typically caused by genetic abnormalities that impact the glomerular basement membrane or podocytes, while it is rarely linked to congenital infections. Nephrotic nephrosis can be caused by a wide range of underlying etiologies in addition to the congenital form of SN, such as glomerular diseases, vasculitis, infections, poisons, cancers, genetic abnormalities, and, most frequently, unidentified reasons. Children with SN should be treated in hospital for the purpose of diagnosis, evaluation and dietary management, edema management, initiation of steroid treatment, and education of parents. Before treating children with SN, anthropometric measurements should be taken to assess nutritional status and blood pressure, check for signs of systemic diseases such as lupus, and look for foci of infection.^{3,7}

Nitric Oxide And eNOS

The short-lived gaseous free radical nitric oxide (NO) has been considered an air contaminant. The nitric oxide synthase (NOS) family is the most investigated and possibly most important biological generator of NO and this enzyme produces NO by oxidizing L-arginine. NOS enzymes have relevance in several physiological contexts, according to biochemical, genetic, and phylogenetic investigations. There are three specific NOS isoforms found in mammals: neuronal (nNOS or NOS I), inducible (iNOS or NOS II), and endothelial (eNOS or NOS III).^{8,9,10}

Neurons, skeletal muscle, and renal macula densa all constitutively express nNOS (NOS1), which produces low amounts of NO in a calcium/calmodulin-dependent way to mediate neurotransmission, synaptic plasticity, and tubuloglomerular feedback for GFR regulation. Cytokines and LPS induce iNOS expression in

macrophages and inflammatory tissues, resulting in high sustained NO without the need for calcium to support inflammation, pathogen destruction, and immunological defense. In vascular endothelial cells and kidney glomeruli, eNOS (NOS3) is constitutively active. It produces tonic low NO through calcium, shear stress and phosphorylation to control blood pressure, vasodilation, platelet aggregation, and renal natriuresis.^{11,12}

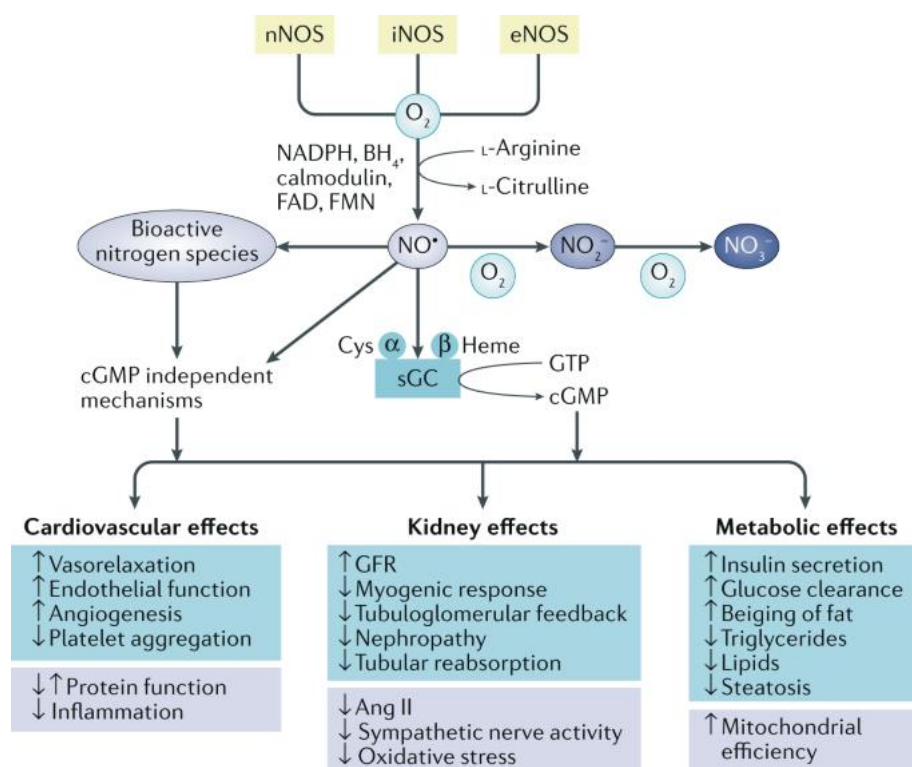


Figure 1. The role of nitric oxide (NO). The NO pathway and possible effects of NO on cardiovascular, renal, and metabolic systems¹⁰

The oxygenase/reductase enzymes of Nitric Oxide Synthase (NOS) (nNOS, iNOS, and eNOS) utilize NADPH, BH_4 (tetrahydrobiopterin), FAD, FMN, calmodulin, heme, and O to transform L-arginine into bioactive NO and L-citrulline. Without the involvement of the NOS system, other pathways produce reactive oxygen/nitrogen species (O_2 , NO_2 , $ONOO^-$), including NO. Both cGMP-dependent and cGMP-independent processes are linked to signaling through these nitrogen species. NO has the following effects in the kidney: prevents tubular salt reabsorption, reduces tubuloglomerular feedback, and maintains the glomerular filtration rate.^{10,11,12}

Quantitative comparison (rough peak levels): $iNOS > nNOS > eNOS$. eNOS produces the lowest tonic NO (picomolar range) for precise vascular homeostasis; this situation is strictly regulated by shear stress, phosphorylation, and nitrogen storage in caveolae, ensuring brief physiological bursts during vasodilation without causing tissue damage. While iNOS produces high-output responses, nNOS/eNOS provides physiological signaling; all catalyze L-arginine to NO and L-citrulline, although their functions distinct in subcellular targeting and mechanism of action.^{11,12}

The presence of nNOS in the macula densa and eNOS in the renal blood vessels has been repeatedly reported; other studies reveal eNOS expression in tubular epithelial cells. The majority of nephron segments, including the proximal tubule, thick ascending limb of the loop of Henle, macula densa, distal tubule, and collecting duct, have been reported to express nNOS protein and mRNA in healthy human kidney tissue samples. Only the endothelium expressed eNOS and enzyme activity tests verified revealed the cortex has higher levels of NOS expression than the medulla.^{13,14}

The kidney expresses all of three specific NOS isoforms (nNOS, iNOS, and eNOS) constitutively. eNOS expression is high in the endothelial layer of arterioles and renal capillaries and in the epithelial cells of the collecting ducts, while nNOS expression is high in the macula densa but lower in intrarenal neurons, efferent arterioles, thick epithelial cells of the ascending limb, and mesangial cells. Interstitial mesangial cells, medullary cells, vascular smooth muscle cells, and epithelial cells in the thick ascending limb, proximal tubule, and collecting duct also express iNOS. A specific decrease in eNOS expression in NS disrupts low-level renal NO production, causing sodium retention despite normal iNOS/nNOS expression.^{11,12,14}

There remains a controversy on NO's precise function in kidney disease. NO metabolite levels in urine were higher in SRNS than in SSNS. NO metabolite levels in urine increased 3.0 times in SSNS and 4.2 times in SRNS relapse group in comparison with the control population. Urinary NO metabolites persisted to be elevated in both groups during remission. According to another report, children with minimal change nephrotic syndrome excreted higher nitrite in their urine, a stable product of NO. It is uncertain how elevated urine nitrite excretion contributes to the disease's clinical symptoms in the children in this group. Considering there were no differences between patients with focal segmental glomerulosclerosis and control subjects, elevated urine nitrite excretion in Minimal-Change nephrotic syndrome cannot be linked to the nephrotic syndrome itself. The persistent rise in nitrite excretion during relapse and remission raises the possibility that renal NO production contributes to minimal-change nephrotic syndrome rather than modulating proteinuria.^{13,14}

Immunological and Genetic Disorders Associated with Nephrotic Syndrome

SSNS patients may have challenging to manage steroid dependence and/or frequent relapses (SDNS/FRNS). Significant morbidity, treatment failure, and recurrent relapses are frequently caused by infections. Randomized clinical trials have shown that levamisole keeps FRNS patients from relapsing and increases their relapse-free period. Classical HLA class II molecules are highly polymorphic heterodimeric transmembrane proteins which are encoded by the HLA-II gene on chromosome 6. A crucial stage in the development of particular CD4⁺T cells in the adaptive immune response is the presentation of foreign antigens in HLA class II molecules by professional antigen-presenting cells. This mechanism of antigen processing and presentation is strongly associated with bacterial or viral infections.^{15,16,17}

The "a" allele of eNOS4 is strongly linked to lower plasma NO levels. The pathophysiology of human

glomerular disease may involve the eNOS4 a/b tandem repeat number variation (VNTR) polymorphism, which is regarded as a risk factor for progressive kidney disease. Decreased eNOS expression in lupus nephritis and IgA nephropathy patients, suggesting a decrease in eNOS's physiological effects on injured glomeruli. Recent studies have correlated increased NO generation to hyperfiltration and microalbuminuria, two characteristics of Diabetic kidney disease in its early stages. An experimental study showed an increase in intrarenal nNOS production in rats with chronic diabetes, which is an important mechanism in the development of renal hyperfiltration in diabetes. This may be due to suppression of the tubuloglomerular feedback system as a result of excessive nNOS synthesis in the kidneys.^{5,10,18, 19, 20}

Recurrence of SSNS is characterized by the recurrence of proteinuria. The recurrence rate is 60%; though this is depends upon the severity of steroid treatment. The number of recurrences within the first six months following diagnosis is a reliable indicator that the disease might progress further. Based on recent studies, there is no noticeable rise in the frequency of the aa and ab genotypes or alleles in individuals who have more relapses. These findings suggest that the eNOS4 genotype and the recurrence rate in SSNS patients are unrelated.^{3,20}

Table 1. Research related to eNOS in Nephrotic Syndrome

Author, Year	Study Type	Sample / Participants	Population	Main outcomes measured	Main findings	Statistical significance	Main limitation
Ni <i>et al</i> , 2003	Review Article	Rats; n=6 per experimental group	PAN-induced nephrotic syndrome; protein-overload proteinuria; inherited analbuminemia	Urinary NO metabolites, fractional Na excretion, renal iNOS/nNOS/eNOS expression, blood pressure	PAN-induced NS showed reduced fractional Na excretion and reduced renal NOS expression, particularly iNOS and nNOS, with reduced urinary NOx. Proteinuria appeared to be an important mediator of NOS downregulation.	p<0.01 for fractional Na excretion versus controls	Animal model; findings may not be directly generalizable to human pediatric NS.
Bae <i>et al</i> , 2010	Experimental	PAN-induced NS rats; n=8/group for major experimental comparisons	Experimental PAN-induced NS	Urinary Na excretion, Na balance, renal nNOS/eNOS/iNOS expression, urinary NOx, ET-1/ETB receptor	On day 7, nNOS expression and urinary NOx were decreased with sodium retention; nNOS recovered and urinary NOx increased by day 14. eNOS expression did not significantly differ between groups.	nNOS reduction: p<0.05; urinary NOx changes: p<0.05	Experimental animal study; eNOS was not significantly altered, limiting direct conclusions about eNOS.

Ray <i>et al</i> , 2015	Review Article	Not applicable	Nephrotic syndrome	Urinary nitrite excretion	Review supports multifactorial sodium retention in NS, including activation of ENaC by filtered proteases; it provides indirect mechanistic context for NO-related sodium handling.	Not applicable	Review article; does not provide original effect estimates and does not specifically evaluate eNOS.
Ciuntu <i>et al</i> , 2016	Cohort	25 SSNS, 20 SRNS, 20 mixed CGN	Pediatric SSNS and SRNS	eNOS Glu298Asp and nNOS C276T polymorphisms	Urinary NO metabolites increased approximately 3.0-fold in SSNS and 4.2-fold in SRNS during relapse versus controls and remained elevated during remission.	Reported as statistically significant in the original study	Small sample size; heterogeneous disease groups; NO metabolites are indirect measures of NO production.
Elmougy R, 2021	Case Control	98 children with NS and 101 controls	Pediatric NS	eNOS 27-bp VNTR, GSTP1 and IL-10 polymorphisms	eNOS 27-bp VNTR genotype distribution differed between NS and controls. AB and BB genotypes were less frequent in patients: AB 17.2% vs 22.8% (OR 0.19, 95% CI 0.06–0.58) and BB 54.7% vs 70.3% (OR 0.19, 95% CI 0.07–0.50).	AB p=0.0026; BB p=0.0004	Genetic association does not establish causality or demonstrate altered eNOS expression/function.
Niepolski <i>et al</i> , 2024	Cohort	50 hemodialysis patients and 26 healthy controls	ESRD on hemodialysis; not NS-specific	Plasma eNOS, phosphorus, blood pressure	Plasma eNOS was lower in HD patients than controls (0.725 vs 1.46 ng/mL); higher BP was associated with lower plasma eNOS in patients with dyslipidemia.	eNOS comparison p=0.004; phosphorus/eNOS analyses p<0.05	Indirect evidence because participants had ESRD on hemodialysis rather than nephrotic syndrome.

Result

Twenty-one sources were reviewed, comprising narrative review articles, experimental animal studies, cohort studies, and a case-control study, focusing on the role of eNOS and nitric oxide in the pathophysiology of nephrotic syndrome (NS) (Table 1). A consistent pattern emerged: impaired eNOS activity or expression accompanies sodium retention, hypertension, and glomerular damage in NS. Both nNOS and eNOS expression decreased during active proteinuria in the puromycin aminonucleoside model, which hindered renal sodium excretion. Interestingly, restoring nNOS and upregulating renal endothelin receptor type B in later stages of the disease improved natriuresis, in line with previous biochemical research that linked NOS downregulation to the severity of proteinuria in NS ^{11,17,20}.

Clinical and mechanistic reviews converged on sodium retention and hypertension as the principal downstream consequences of reduced eNOS-derived NO, disrupting tubuloglomerular feedback and permitting inappropriate tubular sodium reabsorption, alongside a complementary pathway in which filtered serum proteases directly activate epithelial sodium channels (ENaC)¹⁴. A cohort study of urinary NO metabolites found higher excretion in steroid-resistant NS (SRNS) than steroid-sensitive NS (SSNS)²⁰. This pattern appears to be at odds with lower tissue eNOS expression reported elsewhere.

Genetic association studies identified the eNOS4 a/b variable number tandem repeat (VNTR) polymorphism as a recurrent risk marker, with the eNOS4 “a” allele linked to lower plasma NO and the eNOS 27-bp VNTR genotype proposed as a candidate marker for early NS prediction¹⁹; related polymorphism studies reported associations with NS risk in children¹ and with minimal change NS without a clear relationship to relapse frequency, while a comparable eNOS polymorphism (Glu298Asp) has independently been associated with diabetic nephropathy susceptibility^{6, 13, 21, 21}. The eNOS–hypertension link was extended to systemic blood pressure regulation in advanced kidney disease as a cohort of dialysis patients revealed that lower circulating eNOS concentrations were correlated with increased systolic and diastolic blood pressure⁵.

Discussion

These findings converge on eNOS as an active contributor to the sodium retention and hypertension that define NS, rather than a bystander. Under physiological conditions eNOS-derived NO acts as an endogenous diuretic that limits tubular sodium reabsorption and modulates tubuloglomerular feedback; when eNOS activity falls, as shown experimentally and inferred from proteinuria-associated NOS downregulation in humans, this natriuretic brake is lost. This mechanism operates alongside, rather than instead of, protease-mediated ENaC activation, indicating that NS-associated sodium retention is multifactorial. The persistent elevation of urinary NO metabolites despite reduced tissue eNOS expression is reconcilable if compensatory iNOS upregulation in injured tissue offsets the eNOS deficit at the level of total urinary output, or if oxidative stress diverts NO toward peroxynitrite formation, so that elevated NO generation coexists with reduced bioavailable, functional NO^{8-12, 20}. Under either explanation, urinary NO metabolite concentration alone is an unreliable proxy for eNOS activity and should not be read as evidence against a role for eNOS dysfunction in NS.

The genetic data add a further layer of interpretation. The eNOS4 a/b VNTR and Glu298Asp variants recur across NS, IgA nephropathy, lupus nephritis, and diabetic nephropathy, suggesting a shared genetic susceptibility pathway across glomerular diseases rather than one specific to NS^{1, 6, 13, 18}. However, the absence of a consistent association between eNOS4 genotype and relapse frequency in SSNS indicates that eNOS genetic variation may influence susceptibility to disease onset or sodium-retentive complications without determining steroid-responsiveness or relapse behavior, so eNOS genotyping is unlikely to replace existing relapse-prediction markers but could still help identify children at elevated risk of hypertension or progressive kidney injury²⁰. The dialysis-cohort association between lower circulating eNOS and higher blood pressure, taken together with the endothelial and thrombotic consequences of NS-associated endothelial injury, points to eNOS as a mechanistic bridge between glomerular protein leak, endothelial dysfunction, and cardiovascular risk across the course of NS, not solely a determinant of acute edema^{4, 5}.

These conclusions should be weighed against a fragmented evidence base: much of the mechanistic support rests on a single experimental model and on narrative reviews rather than original human data, the identified clinical studies are heterogeneous in design and NS subtype, and few were conducted specifically in pediatric populations despite SSNS being predominantly a childhood disease^{7,8,12,14,17}. No reviewed study combined eNOS4 genotyping, tissue or plasma eNOS measurement, and urinary NO metabolites within the same pediatric cohort. Prospective pediatric studies that pair these measures with longitudinal sodium balance and blood pressure data, together with mechanistic work distinguishing eNOS- from iNOS-derived urinary NO, would clarify these relationships; and given the natriuretic and vasodilatory actions of eNOS-derived NO, interventions that restore eNOS activity or NO bioavailability, such as L-arginine or tetrahydrobiopterin supplementation, antioxidant strategies limiting peroxynitrite formation, or agents upregulating endothelial NOS expression, warrant evaluation as adjunctive approaches to managing edema, relapse, and long-term cardiovascular risk in children with NS^{8-10,12}.

Conclusion

Overall, the available evidence indicates that dysregulation of the eNOS–NO pathway may contribute to the pathophysiology of nephrotic syndrome, particularly through altered renal sodium handling, natriuresis, vascular tone, and blood pressure regulation. Experimental studies support reduced NOS-related signaling in nephrotic syndrome, while clinical studies demonstrate increased urinary NO metabolites and genetic associations involving eNOS polymorphisms. However, these findings are heterogeneous and do not establish a consistent relationship between tissue eNOS expression, NO bioavailability, urinary NO metabolites, and clinical disease activity. Importantly, urinary NO metabolites should not be considered a direct surrogate of eNOS activity because they may reflect NO generated by multiple NOS isoforms and compensatory mechanisms. Therefore, eNOS represents a plausible mechanistic and potential therapeutic target in nephrotic syndrome, but further well-designed pediatric studies integrating eNOS expression or activity, NO bioavailability, genetic variants, urinary NO metabolites, sodium balance, blood pressure, and clinical outcomes are required before eNOS-directed therapy can be recommended.

Conflict of Interest

No conflict of interest exists.

Acknowledgments

None declare

List of Abbreviations

NS: Nephrotic Syndrome; NOS: Nitric Oxide Synthase; SSNS: Steroid-Sensitive NS; eNOS: endothelial NOS; SDNS/FRNS: Steroid Dependence and/or Frequent Relapses Nephrotic Syndrome; ENaC: Epithelial Na Channels.

References

1. Duicu C, Tripon F, Crauciuc A, et al. Endothelial nitric oxide synthase gene polymorphisms and risk of nephrotic syndrome in children. *Arch Dis Child*. 2017;102:A50-A51.
2. Roy RR, Tonny RT, Akbar R, Sultana N, Ali A, Ray AK, et al. Clinicopathological spectrum and response pattern of adolescent-onset idiopathic nephrotic syndrome: are they different from young children? *Paediatr Nephrol J Bangladesh*. 2021;6(2):86-95. doi:10.4103/pnjb.pnjb_24_21.
3. Tapia C, Bashir K. Nephrotic syndrome. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024.
4. Chen G, Liu H, Liu F. A glimpse of the glomerular milieu: from endothelial cell to thrombotic disease in nephrotic syndrome. *Microvasc Res*. 2013;89:1-6. doi:10.1016/j.mvr.2013.06.011.
5. Niepolski L, Malinowska-Loba K. Association of circulating endothelial nitric oxide synthase levels with phosphataemia in patients on haemodialysis. *Biomedicines*. 2024;12(3):687. doi:10.3390/biomedicines12030687.
6. Alasehirli B, Balat A, Barlas O, Kont A. Nitric oxide synthase gene polymorphisms in children with minimal change nephrotic syndrome. *Pediatr Int*. 2009;51:75-78. doi:10.1111/j.1442-200X.2008.02655.x.
7. Tamura H. Trends in pediatric nephrotic syndrome. *World J Nephrol*. 2021;10(5):88-100. doi:10.5527/wjn.v10.i5.88.
8. Navasardyan I, Bonavida B. Regulation of T cells in cancer by nitric oxide. *Cells*. 2021;10(10):2655. doi:10.3390/cells10102655.
9. Niedbala W, Cai B, Liew FY. Role of nitric oxide in the regulation of T cell functions. *Ann Rheum Dis*. 2006;65(Suppl 3):iii37-iii40. doi:10.1136/ard.2006.058446.
10. Carlström M. Nitric oxide signalling in kidney regulation and cardiometabolic health. *Nat Rev Nephrol*. 2021;17(9):575-590. doi:10.1038/s41581-021-00429-z.
11. Ni Z, Vaziri ND. Downregulation of nitric oxide synthase in nephrotic syndrome: role of proteinuria. *Biochim Biophys Acta*. 2003;1638(2):129-137. doi:10.1016/S0925-4439(03)00061-9.
12. Tran N, Garcia T, Anika M, Ali S, Ally A, Nauli SM. Endothelial nitric oxide synthase (eNOS) and the cardiovascular system: in physiology and in disease states. *Am J Biomed Sci Res*. 2022;15(2):153-177.
13. Zhou TB, Xu HL, Yin SS. Association between endothelial nitric oxide synthase Glu298Asp gene polymorphism and diabetic nephropathy susceptibility. *Ren Fail*. 2013;35(1):173-178. doi:10.3109/0886022X.2012.734939.
14. Ray EC, Rondon-Berrios H, Boyd CR, Kleyman TR. Sodium retention and volume expansion in nephrotic syndrome: implications for hypertension. *Adv Chronic Kidney Dis*. 2015;22(3):179-184. doi:10.1053/j.ackd.2014.11.006.
15. Pitt B, Byington RP, Furberg CD, et al. Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. *Circulation*. 2000;102(13):1503-1510. doi:10.1161/01.CIR.102.13.1503.
16. Hackl A, et al. The role of the immune system in idiopathic nephrotic syndrome. *Mol Cell Pediatr*. 2021;8(1). doi:10.1186/s40348-021-00128-6.
17. Mount PF, Power DA. Nitric oxide in the kidney: functions and regulation of synthesis. *Acta Physiol*. 2006;187:433-446. doi:10.1111/j.1748-1716.2006.01582.x.
18. Bae EH, Kim SW. Changes in endothelin receptor type B and neuronal nitric oxide synthase in puromycin aminonucleoside-induced nephrotic syndrome. *Korean J Physiol Pharmacol*. 2010;14(4):223-228. doi:10.4196/kjpp.2010.14.4.223.
19. Elmougy R. Genetic studies of nephrotic syndrome in Egyptian children. *J Appl Biomed*. 2021;19(4):228-233. doi:10.32725/jab.2021.022.
20. Ciuntu A. Role of metabolites of nitric oxide and arginase in the pathogenesis of glomerulonephritis. *Curr Health Sci J*. 2016;42(3):221-225. doi:10.12865/CHSJ.42.03.01.
21. Kameritsch P, et al. The mitochondrial thioredoxin reductase system (TrxR2) in vascular endothelium controls peroxynitrite levels and tissue integrity. *Proc Natl Acad Sci U S A*. 2021;118(7):e1921828118

Original article

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Serum Uric Acid and Glycemic Control among Diabetes Mellitus Patients in Semarang, Indonesia: A Hospital-Based Cross-Sectional Study

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ABSTRACT

Introduction: The relationship between serum uric acid (SUA) and glycemic status in established diabetes is biologically plausible but inconsistent across studies because insulin resistance, renal urate handling, glycosuria, obesity, kidney function, and glucose-lowering therapy can influence SUA in different directions. This study evaluated the association of SUA with fasting blood glucose (FBG) and glycated hemoglobin (HbA1c) in a hospital-based sample in Semarang, Indonesia.

Methods: This retrospective cross-sectional study screened 410 medical records from Sultan Agung Islamic Hospital, Semarang, during 2018–2020. Thirty records with complete SUA, FBG, and HbA1c data were available for analysis. Hyperuricemia was defined as SUA >7.0 mg/dL in men and >6.0 mg/dL in women. The revision reanalyzed the available raw dataset using Shapiro–Wilk testing, Spearman correlation, exploratory partial Spearman correlation adjusted for age, sex, and recorded obesity status, and Fisher's exact test. Two-sided $p < 0.05$ was considered statistically significant.

Results: The mean age was 54.3 ± 6.5 years; 16/30 (53.3%) were women and 18/30 (60.0%) met the sex-specific definition of hyperuricemia. SUA showed a moderate positive monotonic association with FBG (Spearman $\rho = 0.401$, 95% bootstrap CI 0.053 to 0.665, $p = 0.028$); this remained similar after adjustment for age, sex, and obesity (partial $\rho = 0.396$, $p = 0.041$). The association with HbA1c was weak and not statistically significant ($\rho = 0.270$, 95% bootstrap CI -0.126 to 0.624, $p = 0.149$).

Conclusion: Higher SUA was associated with higher FBG, but not HbA1c. These exploratory findings should be interpreted cautiously because of the small, highly selected sample and incomplete data on renal function, medication use, diabetes duration, and other confounders.

Keywords: Diabetes mellitus; fasting blood glucose; HbA1c; hyperuricemia



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Introduction

Diabetes mellitus (DM) refers to a wide range of metabolic disorders that share underlying commonality with hyperglycemia. It could occur in different ways and impacts the body differently, either through autoimmune destruction of β -cells of the pancreas or progressive resistance to insulin despite a degree of insulin insufficiency. Due to the chronic nature of this condition and because it affects the whole body, DM has to be regularly monitored, observed, and managed throughout the patient's life, given that healthcare systems are significantly strained by the burden of diabetes mellitus and its complications.^{1,2} Central to the development of these complications is persistent hyperglycemia, which drives progressive damage due to a wide range of mechanisms most of which include oxidative stress, the inflammatory pathway, the production of advanced glycosylation end products, and alterations in the endothelial function.³ Due to this, hyperglycemia is considered a hallmark of the disease and can be used for its diagnosis and monitoring. Prolonged elevated blood glucose levels are associated with an increased risk of both microvascular and macrovascular complications, contributing to morbidity and mortality in affected individuals, and are known to damage a range of vital organs including the eyes, kidneys, heart, and nerves.^{1,2}

Diabetes mellitus (DM) remains a major global health challenge, with prevalence projected to reach 783 million cases by 2045⁴. Poor glycemic control, reflected by elevated fasting blood glucose (FBG) and glycated hemoglobin (HbA1c), is strongly associated with increased risks of microvascular and macrovascular complications, making optimization of metabolic control a central goal of diabetes management^{5,6}. The increasing prevalence of diabetes is driven by a combination of many factors, among them demographic shifts and aging populations, sedentary lifestyles, and increasingly rising rates of obesity. Low- and middle-income countries currently account for a notable and growing share of the total global diabetes burden, where delayed diagnosis and often severely limited access to comprehensive care frequently culminate in suboptimal glycemic control levels. In such settings, the routine use of laboratory markers plays an exceptionally important role in guiding clinical decision-making. Therefore, it is imperative to underscore the necessity for better understanding the precise factors influencing glycemic status,⁷⁻⁹ In this context, there is an urgent need to identify additional metabolic factors that may influence glycemic control or serve as accessible markers to improve risk stratification and clinical decision-making.

In recent years, the role of serum uric acid levels as a modifiable risk factor of type 2 DM has attracted considerable attention. Hyperuricemia has been widely observed in patients with type 2 DM, especially those with insulin resistance and metabolic syndrome¹⁰. Clinical trials and experimental studies have suggested a bidirectional relationship, whereby insulin resistance can affect the renal clearance of uric acid, thereby increasing serum uric acid levels, while increased uric acid levels can induce endothelial dysfunction, oxidative stress, and inflammation that further enhance insulin resistance and cardiovascular risk.^{11,12}. This immediately raises a pertinent question: whether serum uric acid primarily reflects an individual's glycemic control status or independently contributes to the documented adverse metabolic outcomes.

Despite these uncertainties, data from hospitals in Indonesia itself are still limited. Moreover, the clinically relevant question for a cross-sectional hospital study is therefore not whether uric acid causes adverse metabolic outcomes, but whether a routinely measured SUA value tracks concurrent glycemic status in the local clinical population. Indonesian hospital-based data addressing this narrower question are limited, and previous reports have produced positive, negative, and null associations. This study aimed to estimate the direction, magnitude, and precision of the association between SUA and two glycemic markers—FBG and HbA1c—among patients whose records were available at Sultan Agung Islamic Hospital, Semarang, during 2018–2020.

Methods

This retrospective observational study used a cross-sectional design and medical-record data from Sultan Agung Islamic Hospital, Semarang, Indonesia, during 2018–2020.

A total of 410 records were screened using consecutive record sampling. Records were eligible for the analytic dataset when SUA, FBG, and HbA1c results were available within the study period. Records with incomplete or missing data for one or more of these three laboratory variables were excluded, leaving 30 complete records for analysis. The archived extraction did not permit a more detailed classification of the missing-data pattern among the 380 excluded records. Because this was a retrospective complete-case analysis, the analytic sample was determined by data availability rather than by an a priori sample-size calculation. Additional exclusions based on chronic kidney disease, gout, urate-lowering therapy, diuretics, SGLT2 inhibitors, or other medications could not be consistently applied because these variables were not retained in the available research extraction.

SUA was recorded in mg/dL. Hyperuricemia was defined as SUA >7.0 mg/dL in men and >6.0 mg/dL in women, consistent with the original study protocol. FBG was recorded in mg/dL and categorized as elevated when >126 mg/dL. HbA1c was recorded as a percentage and categorized as elevated when >6.5%. Age, sex, systolic and diastolic blood pressure, and recorded obesity status were also abstracted when available. The source summary categorized 24 patients as hypertensive and 6 as non-hypertensive; exact BMI values, diabetes duration, renal-function indices, and complete medication histories were not available.

SUA, FBG, and HbA1c measurements were extracted from routine hospital laboratory records. The archived research dataset did not preserve the analyzer model, analytical principles, calibration data, or internal and external quality-control records; these assay-specific details therefore could not be reconstructed retrospectively.

Continuous variables were summarized using mean±standard deviation or median and interquartile range, as appropriate, and categorical variables using frequency and percentage. Given the small sample and marginal normality of FBG, Spearman rank correlation was used as the primary association analysis. Ninety-five percent confidence intervals (CIs) for Spearman coefficients were estimated with 20,000 bootstrap

resamples. Exploratory partial Spearman correlations were calculated, adjusting for age, sex, and recorded obesity status. Pearson correlation was retained as a sensitivity analysis to facilitate comparison with the original analysis. Fisher exact tests compared elevated FBG and elevated HbA1c between hyperuricemic and non-hyperuricemic groups. Statistical analyses were performed using Python 3.13 with SciPy and statsmodels. All tests were two-sided and $P < .05$ was considered statistically significant.

The study was approved by the Bioethics Commission for Medical and Health Research, Faculty of Medicine, Universitas Islam Sultan Agung, Semarang (approval No. 56/EC/KEPK/2020). All patient data were anonymized before analysis.

Results

Of 410 screened medical records, 30 complete records (7.3%) were included in the analysis. The remaining 380 records were excluded because one or more required laboratory variables were incomplete or missing (Figure 1).

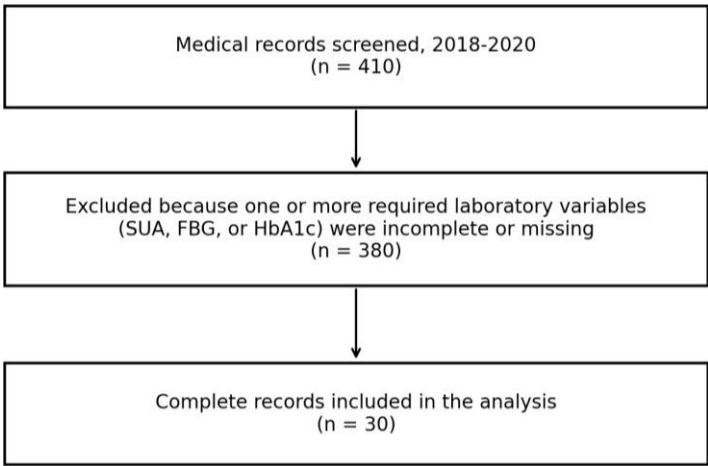


Figure 1. Flow diagram of record selection

The mean age was 54.3 ± 6.5 years; 16 patients (53.3%) were women. Eighteen records (60.0%) met the sex-specific definition of hyperuricemia. Nineteen records (63.3%) had elevated FBG, and 19 (63.3%) had elevated HbA1c. Baseline characteristics are summarized in Table 1.

Table 1. Baseline characteristics of the analyzed records (n=30)

Characteristic	Value
Age, years	54.3 ± 6.5
Women	16 (53.3%)

Characteristic	Value
Men	14 (46.7%)
Serum uric acid, mg/dL	6.95 ± 2.13
Hyperuricemia	18 (60.0%)
Systolic blood pressure, mmHg	154.8 ± 33.5
Diastolic blood pressure, mmHg	89.5 ± 21.1
Hypertension, as reported in source summary	24 (80.0%)
Obesity, recorded	6 (20.0%)
FBG, mg/dL	149 (104.8-189.5)
Elevated FBG (>126 mg/dL)	19 (63.3%)
HbA1c, %	7.12 ± 1.79
Elevated HbA1c (>6.5%)	19 (63.3%)

Values are mean ± standard deviation, median (interquartile range), or n (%). FBG, fasting blood glucose; HbA1c, glycated hemoglobin. Exact BMI values, diabetes duration, renal-function indices, and medication histories were unavailable.

SUA showed a moderate positive monotonic association with FBG (Spearman rho=0.401, 95% CI 0.056 to 0.666; P=0.028). After adjustment for age, sex, and recorded obesity, the association remained similar (partial rho=0.396; P=0.041). The association between SUA and HbA1c was weak and not statistically significant (rho=0.270, 95% CI -0.131 to 0.626; P=0.149) (Table 2).

Table 2. Association between serum uric acid and glycemic parameters

Outcome	Spearman rho	95% CI	P	Partial rho*	P
FBG	0.401	0.056 to 0.666	0.028	0.396	0.041
HbA1c	0.270	-0.131 to 0.626	0.149	0.269	0.174

Exploratory partial Spearman correlation adjusted for age, sex, and recorded obesity status. CI, confidence interval; FBG, fasting blood glucose; HbA1c, glycated hemoglobin.

As a sensitivity analysis, Pearson correlation yielded $r=0.317$ ($P=0.088$) for SUA-FBG and $r=0.278$ ($P=0.137$) for SUA-HbA1c. Scatter plots are shown in Figure 2.

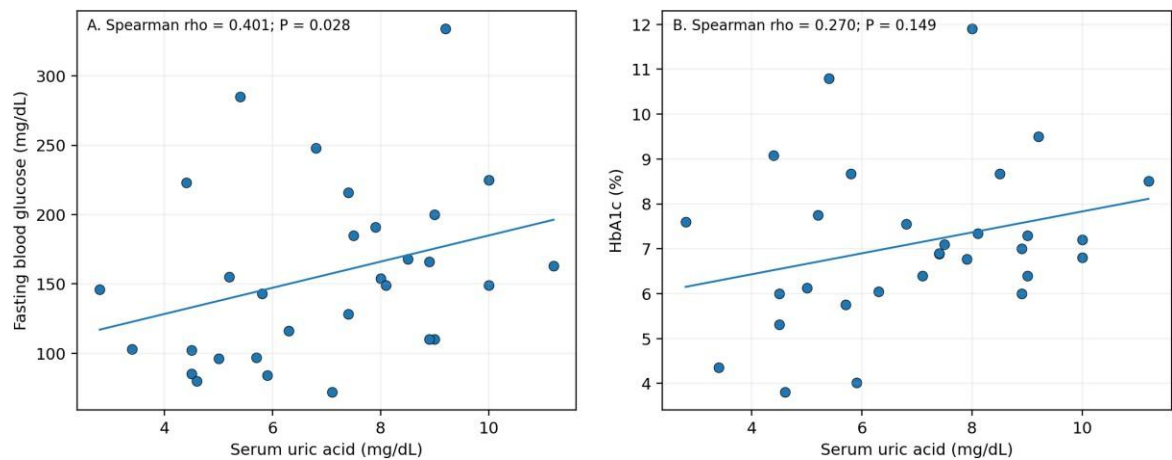


Figure 2. Scatter plots of serum uric acid with (A) fasting blood glucose and (B) HbA1c

Elevated FBG was present in 14 of 18 hyperuricemic patients (77.8%) compared with 5 of 12 non-hyperuricemic patients (41.7%). The same distribution was observed for elevated HbA1c. These categorical differences did not reach the conventional significance threshold (Fisher exact $P=.063$ for each comparison) (Table 3).

Table 3. Glycemic categories according to hyperuricemia status

Glycemic parameter	Hyperuricemia (n=18)	No hyperuricemia (n=12)	Fisher P
Elevated FBG	14 (77.8%)	5 (41.7%)	0.063
Elevated HbA1c	14 (77.8%)	5 (41.7%)	0.063

FBG, fasting blood glucose; HbA1c, glycated hemoglobin

Discussion

The main finding was a modest positive monotonic association between SUA and FBG, while the association with HbA1c was weak and not statistically significant. The FBG association remained similar after limited adjustment for age, sex, and recorded obesity. The categorical analysis also showed a higher proportion of elevated FBG and HbA1c among hyperuricemic patients, although these comparisons narrowly missed the conventional significance threshold. Because only 30 complete records were analyzed, these estimates should be interpreted as exploratory rather than definitive.

The biological relationship between uric acid and glucose is not expected to be uniform across all stages of dysglycemia. Hyperinsulinemia can increase renal urate reabsorption, whereas marked hyperglycemia can promote glycosuria and uricosuria. Wei et al. reported that SUA and HbA1c may change dynamically during the development of type 2 diabetes, and Shi et al. described an inverted-U

relationship between SUA and fasting glucose across non-diabetic, prediabetic, and diabetic states^{13–15}. These mechanisms may partly explain why the present study identified an association with FBG but not with HbA1c.

Previous clinical studies have also reported inconsistent directions of association. Patel et al. observed inverse correlations between SUA and both HbA1c and fasting glucose among participants with diabetes, while a meta-analysis of urate-lowering interventions found a reduction in fasting glucose overall but no clear HbA1c benefit and no consistent glycemic benefit in diabetic subgroups^{16,17}. This heterogeneity supports the interpretation that SUA is strongly influenced by metabolic stage and coexisting clinical factors and should not be considered a direct substitute for standard glycemic markers.

Renal function and medication exposure are particularly important potential confounders. Higher blood glucose can promote uric acid excretion, while SGLT2 inhibitors lower SUA through uricosuric mechanisms; impaired kidney function can further modify urate handling^{18–20}. The present analysis could adjust only for age, sex, and recorded obesity. Information on renal function, gout, urate-lowering therapy, diuretics, SGLT2 inhibitors, diabetes duration, and other glucose-lowering treatment was not sufficiently available for adjustment. Residual confounding is therefore likely.

This study has several limitations. Only 30 of 410 screened records were complete, creating substantial potential for selection bias. The specific pattern and mechanism of missingness among the 380 excluded records could not be reconstructed. With $n=30$, the study has approximately 80% power only for relatively large correlations of about $|r|=0.49$ or greater, so smaller true associations may be missed. Exact BMI, renal-function measures, diabetes duration, and medication data were unavailable, and assay-specific analyzer and quality-control information could not be recovered from the archived research extraction. The cross-sectional design also prevents conclusions about temporality or causality.

Clinically, FBG and HbA1c remain the appropriate validated measures of glycemic status. The present findings suggest that SUA may covary with FBG in some hospital-based patients, but the small sample and incomplete confounder information prevent use of SUA as an independent marker of glycemic control. Larger studies with explicit eligibility criteria, complete renal and medication data, and adequately powered multivariable analyses are required.

Conclusion

In this small and highly selected hospital-based sample, higher serum uric acid was modestly associated with higher fasting blood glucose after limited adjustment for age, sex, and recorded obesity, whereas no statistically significant association was found with HbA1c. These findings are exploratory and do not establish serum uric acid as an independent marker of glycemic control. Larger studies with complete renal-function and medication data are needed.

Conflicts of Interest

There is no conflict of interest.

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References

1. Lu Y, Wang W, Liu J, Xie M, Liu Q, Li S. Vascular complications of diabetes: A narrative review. *Medicine*. 2023;102(40):e35285. doi:10.1097/MD.00000000000035285
2. Banday MZ, Sameer AS, Nissar S. Pathophysiology of diabetes: An overview. *Avicenna J Med*. 2020;10(4):174. doi:10.4103/AJM.AJM_53_20
3. González P, Lozano P, Ros G, Solano F. Hyperglycemia and Oxidative Stress: An Integral, Updated and Critical Overview of Their Metabolic Interconnections. *International Journal of Molecular Sciences* 2023, Vol 24, Page 9352. 2023;24(11):9352. doi:10.3390/IJMS24119352
4. International Diabetes Federation. *IDF Diabetes Atlas 10th Edition*. 2021. www.diabetesatlas.org
5. PERKENI. GUIDELINES FOR INDEPENDENT BLOOD GLUCOSE MONITORING 2019 (1st ed.). Published online 2019.
6. Committee ADAPP. 2. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes—2024. *Diabetes Care*. 2023;47(Supplement_1):S20-S42. doi:10.2337/dc24-S002
7. McBrien KA, Naugler C, Ivers N, et al. Barriers to care in patients with diabetes and poor glycemic control—A cross-sectional survey. *PLoS One*. 2017;12(5):e0176135. doi:10.1371/JOURNAL.PONE.0176135
8. Popkin BM. Nutrition Transition and the Global Diabetes Epidemic. *Curr Diab Rep*. 2015;15(9):64-. doi:10.1007/S11892-015-0631-4/METRICS
9. Ali I. Urbanization and the Rise of Lifestyle Diseases. *International journal of medical and health sciences archives*. 2024;3(02):88-104. Accessed December 16, 2025. <https://ijmhsa.com/index.php/IJMhSA/article/view/27>
10. Bai Y, Feng Y, Jiang B, et al. The Role of Exercise in Reducing Hyperlipidemia-Induced Neuronal Damage in Apolipoprotein E-Deficient Mice. *Biomed Res Int*. 2021;2021. doi:10.1155/2021/5512518
11. Hisatome I, Li P, Taufiq F, et al. Hyperuricemia as a Risk Factor for Cardiovascular Diseases. *Journal of Biomedicine and Translational Research*. 2020;6(3):101-109. doi:10.14710/JBTR.V6I3.9383
12. Fan Z, Bin L. Will Sirtuin 2 Be a Promising Target for Neuroinflammatory Disorders? *Front Cell Neurosci*. 2022;16:915587. doi:10.3389/FNCEL.2022.915587/FULL
13. Shi H, Liu Y, Yang D, et al. Inverted U-shaped associations between serum uric acid and fasting - plasma glucose level in non-diabetic, pre-diabetic, and diabetic adults: A population-based study in China. *J Diabetes Investig*. 2023;15(4):483. doi:10.1111/JDI.14132
14. Wei F, Chang B, Yang X, Wang Y, Chen L, Li WD. Serum Uric Acid Levels were Dynamically Coupled with Hemoglobin A1c in the Development of Type 2 Diabetes. *Sci Rep*. 2016;6. doi:10.1038/SREP28549
15. Hasan M, Mohieldein A. In Vivo Evaluation of Anti Diabetic, Hypolipidemic, Antioxidative Activities of Saudi Date Seed Extract on Streptozotocin Induced Diabetic Rats. *J Clin Diagn Res*. 2016;10(3):FF06. doi:10.7860/JCDR/2016/16879.7419
16. Patel S, Singh M, Kahlon N. Association of serum uric acid levels with glycated haemoglobin in diabetic

- patients and healthy controls. *J Family Med Prim Care*. 2024;13(11):5040. doi:10.4103/JFMPC.JFMPC_777_24
17. Chen J, Ge J, Zha M, Miao JJ, Sun ZL, Yu JY. Effects of Uric Acid-Lowering Treatment on Glycemia: A Systematic Review and Meta-Analysis. *Front Endocrinol (Lausanne)*. 2020;11. doi:10.3389/FENDO.2020.00577
 18. Zhang L, Zhang F, Bai Y, Huang L, Zhong Y, Zhang X. Effects of sodium-glucose cotransporter-2 (SGLT-2) inhibitors on serum uric acid levels in patients with chronic kidney disease: a systematic review and network meta-analysis. *BMJ Open Diabetes Res Care*. 2024;12(1):e003836. doi:10.1136/BMJDRC-2023-003836
 19. Dong M, Chen H, Wen S, et al. The Mechanism of Sodium-Glucose Cotransporter-2 Inhibitors in Reducing Uric Acid in Type 2 Diabetes Mellitus. *Diabetes, Metabolic Syndrome and Obesity*. 2023;16:437-445. doi:10.2147/DMSO.S399343
 20. Zhou Y, Wang H, Gao W. Elevated Blood Glucose Can Promote Uric Acid Excretion: A Cross-Sectional Study Involving Urinary Glucose and Urinary Uric Acid in China. *Diabetes, Metabolic Syndrome and Obesity*. 2024;17:4553-4563. doi:10.2147/DMSO.S472686

Original article

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Impact of Breast-Massage Training on Milk Formation among Third-Trimester Pregnant Women, Sulili Puskesmas-Pinrang 2024

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ABSTRACT

Introduction: Suboptimal milk production is often the reason why mothers stop breastfeeding, one of which is due to the lack of proper stimulation of the breasts. Breast massage, such as lactation massage, has been proven to stimulate the prolactin and oxytocin hormones that play a role in milk production and secretion. This study aims to determine the impact of breast massage training on the process of breast milk formation in third trimester pregnant women.

Methods: This study used a one group pre-test and post-test design with pre-experimental quantitative methods. The sample consisted of 23 third trimester pregnant women who were selected using purposive sampling technique. The research was conducted at the Sulili Health Center, Pinrang Regency, in August-September 2024. Data were collected through questionnaires, skill checklists, and observation of colostrum production before and after training. Data were analyzed using the Wilcoxon non-parametric test.

Results: The results showed a significant increase in mothers' knowledge and skills after breast massage training. Before the training, all respondents had low knowledge and moderate skills. After the training, 100% of respondents reached the high knowledge and skill categories. In addition, colostrum production increased significantly, from 0% before training to 88% after training.

Conclusion: Breast massage training is effective in improving knowledge, skills, and colostrum production in 3rd trimester pregnant women. It is expected that this training can be integrated in routine health education programs for pregnant women to support successful breastfeeding.

Keywords: Breast massage training; milk production; colostrum; 3rd trimester pregnant women



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Introduction

A survey in Indonesia reported that 38% of mothers stopped breastfeeding due to lack of breast milk. Inadequate breast milk makes mothers worried, afraid to breastfeed and has an impact on the baby's laziness to suckle, resulting in a decrease in the production and activity of the hormones oxytocin and prolactin, causing the amount of breast milk to decrease, even causing the milk ducts to block and stagnate, so that mothers gradually stop breastfeeding and switch to formula milk.¹

The World Health Organization (WHO) publishes child growth standards that are then implemented in all regions of the world and the text of the standards emphasizes the importance of breastfeeding from birth to 6 months in infants, meaning that infants are breastfed until they reach 6 months of age without receiving additional liquids and other solid foods. After birth, nutrition plays the most important role in the healthy growth and development of infants. WHO has set a target that by 2025, at least 50% of infants under 6 months of age will be exclusively breastfed. UNICEF data explains that only 32.6% of them are exclusively breastfed for the first 6 months. In developing countries, only 39% of mothers exclusively breastfeed their babies.¹ Based on the routine report of the Directorate General of Public Health in 2022, the achievement of the indicator of infants aged less than 6 months receiving exclusive breastfeeding was 67.96%. This achievement has met the 2022 national target of 50%. However, there are still around 32.04% of infants in Indonesia who are not exclusively breastfed.²

Pinrang Regency Health Office 2021 states that in 2019, it was recorded that babies who received exclusive breastfeeding were 55.89%. Then in 2020 it increased to 86.92% and in May 2021 it was recorded that 79.79% of babies were exclusively breastfed. This indicates that about 20% of children do not get exclusive breastfeeding and there is an increase of about 7% in babies who do not get exclusive breastfeeding from 2020 to 2021.³

According to experts, breast milk is the most perfect food for infant growth and development. Breast milk has a great influence on the health of both mother and baby. One of the efforts to increase breast milk production is breast care. Breast care can be done by massaging the breasts and stimulating the oxytocin reflex. Oxytocin is a hormone that can increase the influx of intracellular calcium ions.⁴

The purpose of this breast care action is so that blood circulation in the breast area becomes smooth and can prevent inhibition of breast milk channels, so that the process of releasing breast milk becomes smooth. The effect of breast milk production and discharge is caused by prolactin and oxytocin hormones. The prolactin hormone affects the amount of breast milk production, and the process of breast milk release is influenced by the hormone oxytocin.⁵

One of the ways to increase breast milk production is by implementing interventions in the form of breast care.⁴ Breast care is maintenance that is done to facilitate breast milk and avoid difficulties during breastfeeding by doing massage.⁴ Breast massage that can be done to facilitate breast milk is lactation massage,

oxytocin massage, Woolwich massage, and oketani massage.⁶

Lactation massage is a massage technique performed on the head or neck, back, spine, and breast area with the aim of stimulating prolactin and oxytocin hormones.⁷ Furthermore, oxytocin massage is an act of spinal massage starting from the ribs to the shoulder blades, which will accelerate the activity of the parasympathetic nerves to send commands to the back of the brain to produce oxytocin.⁸ In addition to oxytocin massage there is also Woolwich massage. Woolwich massage is intended to activate the stimulation of epithelial muscle cells around the breast glands, with the stimulation then traveling to the hypothalamus and can activate the anterior pituitary gland, produce prolactin hormone and produce more breast milk.⁹ Finally, there is oketani massage, which will make the breasts soft and supple and the areola and nipple more elastic. Oketani massage can make the breast glands mature and enlarge, so that the breast glands will produce more breast milk.⁶

Based on the description above related to the lack of breast milk production in mothers and how the effect of breast care, namely massage, can affect breast milk production in third trimester pregnant women, researchers are interested in conducting research on the impact of breast massage training on the process of breast milk formation in third trimester pregnant women, especially at Puskesmas Sulili Pinrang Regency in 2024.

Methods

This research uses a type of quantitative research with experimental methods, namely pre-experiment research. Pre-Experiment is a research method that uses a research group that does not use a control group. In this study, the design used was a one group pre and post test design, which means that two measurements were taken on the same subject by carrying out certain influences or treatments. Before receiving treatment, a pre-test measurement was taken in the research group, then after the research group received treatment, measurements were taken in the research group to determine the effect of the post-test treatment. This study received ethical approval following a submission in August 2024; approval was granted on September 2, 2024, under reference number 446/A.1/KEP-UMI/IX/2024. The research subsequently commenced in September. The research was conducted at the Sulili Health Center, Mamminasae, Paleteang District, Pinrang Regency, South Sulawesi in September 2024. The population taken from this study were trimester 3 pregnant women at the Sulili Health Center, Pinrang Regency with a sample size of 25 people in September. In this study the research variables were identified as independent variables and dependent variables. The independent variable used in this study is the impact of breast massage training. This is a treatment to get or obtain a certain effect. The dependent variable used in this study is the quality of breast milk in third trimester pregnant women seen from the release of colostrum before labor after massage.

Data that has been collected by researchers will be processed using the SPSS (Statistical Package for

the Social Sciences) program. Data analysis was carried out by univariate and bivariate analysis.

Results

This study was conducted in September 2024 and 25 research respondents were obtained. Research on the impact of breast massage training on the process of breast milk formation in 3rd trimester pregnant women at Puskesmas Sulili Pinrang Regency in 2024. The results of this study are presented in 2 data analyses, univariate analysis to determine the distribution of the characteristics of research respondents and bivariate analysis to determine the effect of breast massage training on increasing knowledge and skills and also knowing whether after breast massage is able to release colostrum after massage.

The following are the characteristics of the research subjects involved in this study.

Table 1. Characteristics of the subjects

Category	Frequency	%
Age		
< 20 years	4	16
20 – 35 years	16	64
> 35 years	5	20
Total	25	100%
Education		
Not in School	6	24
Elementary – Junior high school	7	28
Senior High School/ \Vocational School	9	36
College	3	12
Total	25	100%
Jobs		
Housewife	13	52
Self-employed	9	36
Private worker	1	4
Civil servant	2	8
Total	25	100%

Source: Primary Data, 2024

Table 1 shows that this study involved 25 subjects with the majority aged 20-35 years (64%) and the others aged <20 years (16%) and >35 years (20%). In terms of education, most had secondary education (36%),

while 28% had elementary/junior high school education, 24% did not attend school, and only 12% were college graduates. The most common occupation was housewife (52%), followed by self-employed (36%), with a few working as civil servants (8%) and private employees (4%). This data shows that the majority of respondents are of productive age, have a secondary education background, and are mostly engaged in domestic activities or independent businesses.

The results of the study included the level of knowledge, skill level and colostrum production in pregnant women in the third trimester.

Table 2. Knowledge Test Results

Category	Pre-test		Post-test	
	F	%	F	%
Low	25	100%	0	0%
Simply	0	0%	0	0%
High	0	0%	25	100%

Source: Primary Data, 2024

Based on the results of data analysis in the study on the impact of breast massage training on the process of breast milk formation in third trimester pregnant women, there were significant changes in the level of knowledge of pregnant women before and after attending the training. During the pre-test, 100% (25 people) of pregnant women were in the low knowledge category regarding breast milk formation. However, after the training (post-test), there was a significant increase in knowledge, where all participants (100%) reached the high knowledge category. There were no participants in the moderate or low categories in the post-test.

Table 3. Skill Test Results

Category	Pre-test		Post-test	
	F	%	F	%
Low	0	0%	0	0%
Simply	25	100%	0	0%
High	0	0%	25	100%
Total	25	100%	25	100%

Source:Primary Data, 2024

The results of data analysis regarding the skills of trimester 3 pregnant women in skills before and after breast massage training also showed significant changes. At the pre-test stage, all participants (100% or 25 people) had skills in the moderate category. However, after attending the training (post-test), all participants (100%) showed an increase in skills to the high category. No participants were in the low or fair category at the post-

test stage.

Table 4. Statistical Test Results of Colostrum Production

Kategori	Pre-test		Post-test	
	F	%	F	%
No colostrum production	25	100%	3	12%
There is colostrum production	0	0%	22	88%
Total	25	100%	25	100%

Source: Primary Data, 2024

Based on the analysis of colostrum production in 3rd trimester pregnant women before and after breast massage training, there was a significant increase. At the pre-test stage, all participants (100% or 25 people) had not experienced colostrum production. However, after the training (post-test), 88% of the participants (22 people) began to show colostrum production, while the other 12% (3 people) had not experienced any changes.

Discussion

Breast massage training for 3rd trimester pregnant women at Sulili Health Center showed significant improvement in skills, knowledge, and colostrum production. The results of statistical analysis using the Shapiro-Wilk test showed that the pre-test and post-test data on both skills and knowledge were not normally distributed ($p < 0.001$). Therefore, the Wilcoxon non-parametric test was used to test the effectiveness of this training.

In the skills aspect, there was a significant increase after the training. The average pre-test score of participants' skills was 4.48 (SD = 0.509), while in the post-test it increased to 12.64 (SD = 0.568). The Wilcoxon test resulted in $Z = -4.466$ with $p < 0.001$, indicating that the training was successful in improving participants' skills in performing breast massage to support the process of breast milk formation.

The results of this study are in line with the findings presented by Zulfiana et al. regarding the impact of training on the knowledge and skills of breastfeeding mothers. In training I, before education on proper breastfeeding, only 5 out of 16 mothers had good knowledge, while 11 mothers were still in the poor category. In addition, in the lactation massage and oxytocin massage skills training, only 3 mothers showed good skills, while 13 mothers were still unskilled.¹⁰

After training II, which was conducted with a similar approach, there were significant changes. After education on the correct way to breastfeed, all 16 breastfeeding mothers improved their knowledge to the good category. More interestingly, after training on lactation massage and oxytocin massage skills, all participants (16 mothers) demonstrated good skills. This shows that an effective education and training approach can result in dramatic improvements in mothers' knowledge and skills.¹⁰

The results of this study are also in line with the findings of Zuraidah et al., with the subjects used in

the study being midwives. This study showed an increase in knowledge in midwives after education in community service activities. In Zuraidah et al's research, 80% of midwives had sufficient knowledge and 20% were good at the pre-test, but after education, all midwives (100%) showed an increase to the good category.¹¹ Improvement was also seen in participants' knowledge. The pre-test mean score of knowledge was 8.40 (SD = 0.816), and increased to 16.00 (SD = 0.001) in the post-test. The Wilcoxon test resulted in $Z = -4.467$ with $p < 0.001$, indicating that this training significantly improved pregnant women's understanding of breast massage techniques and their benefits in breast milk formation.

The results of a study conducted by Lestarningsih et al. showed a significant increase in the knowledge of breastfeeding mothers regarding breast milk imbalance and oxytocin massage acupressure techniques after health counseling. Before the counseling, the majority of mothers had sufficient (50%) and insufficient (50%) knowledge. However, after the counseling, there was a striking change, where 83.3% of mothers now had very good knowledge.¹²

This finding is in line with the results of a study conducted at the Sulili Health Center, which also found a significant increase in knowledge in third trimester pregnant women after attending breast massage training. Before the training, these women showed a mean pre-test score of 8.40, which then increased to 16.00 after the training. Statistical tests showed that this change was significant ($p < 0.001$), indicating that the training was effective in improving understanding of techniques that support breastmilk formation.

The research conducted by Rihi et al. is also in accordance with stating that the training showed a positive impact of community service activities on the knowledge and ability of pregnant women in breast care. Before the education, only 7 mothers (32%) had good knowledge about breast care, while 11 mothers (50%) had sufficient knowledge and 4 mothers (18%) had poor knowledge. However, after the implementation of health education, there was a significant improvement where all 22 mothers (100%) showed knowledge in the good category. This finding suggests that proper education can improve mothers' understanding of proper breast care techniques and their benefits during breastfeeding.¹³

The most notable improvement was seen in colostrum production. Before the training, none of the participants reported colostrum production (0 out of 25). However, after the training, 22 people (88%) started producing colostrum, while only 3 people (12%) had not yet experienced production. The Wilcoxon test showed a p value < 0.001 , confirming that the breast massage training had a significant impact in stimulating colostrum production.

The results of a study conducted by Mulazimah et al. showed that breast care training for breastfeeding mothers had a significant impact. Of the total 33 mothers involved, 24 people (72.72%) managed to perform breast care independently, while 9 people (27.28%) still did not perform the treatment properly. This study emphasizes that in addition to maternal knowledge and skills in breast care, the smooth flow of breast milk is also very important to achieve exclusive breastfeeding quality.¹⁴

Good breast care is an important action especially during the postpartum period, where mothers need to take care of their breasts to facilitate milk production. According to this study, breast care can be done on days 1 to 3 after childbirth, at least twice a day, with a duration of 30 minutes each before the morning and evening showers. Physiologically, this action stimulates the breast glands to secrete important hormones such as progesterone, estrogen and oxytocin, which contribute to the smooth production of breast milk.¹⁴

These findings are relevant to the results of a study conducted at Sulili Health Center, which showed that breast massage training was effective in improving the skills and knowledge of 3rd trimester pregnant women. Following the training, the women showed significant improvements in knowledge and skills, which resulted in better colostrum production. A total of 22 out of 25 mothers reported starting to produce colostrum after the training, suggesting that education and training can provide the support needed to improve breastfeeding health.

The results of the study are in line with those conducted by Sembiring, which showed a significant change in the fluency of breast milk production in postpartum mothers after the oketani breast milk massage method. Before the intervention, as many as 14 people (87.5%) of the respondents experienced unsmooth breast milk production. This shows that the majority of the studied mothers faced challenges in producing breast milk properly after giving birth.¹⁵

After the massage training, all 16 participating mothers (100%) reported good milk production. This finding confirms that certain massage techniques can effectively improve the smooth production of breastmilk in postpartum mothers. This intervention provides evidence that massage is not only a physical practice, but also a method that has the potential to improve breastfeeding outcomes for mothers.¹⁵

Literature sources also suggest that other methods can be valuable additions to support pregnant and breastfeeding mothers. For example, endorphin massage training can help promote relaxation and reduce stress, which are important factors in increasing milk production. This massage technique not only focuses on the physical aspect, but also pays attention to the emotional well-being of the mother, thus creating an environment that is more conducive to breastfeeding.¹⁶

Breastfeeding counseling training is also highly recommended. Breastfeeding counseling provides the necessary support for mothers to understand proper breastfeeding techniques and how to overcome any problems they may face. With this approach, mothers not only gain theoretical knowledge, but also emotional support that can help them feel more confident during the breastfeeding period.¹⁷

Lactation massage is a massage that is often used in breast care efforts in preparation for breastfeeding in pregnant women. This massage is done on the nape (neck) area, back, spine (shoulder blades), and also on the breasts whose purpose is to stimulate the hormones oxytocin and prolactin. Lactation massage can increase breast milk production in mothers. The massage is done when the breast is normal, swollen, or not smooth, and in cases where the mother wants to relax, it is assisted by massage on certain parts of the body which has a

positive impact on the condition of the mother's mind and body, giving a calming effect, normalizing blood circulation, and increasing milk supply.¹⁸

Breast massage should also be done with the correct massage technique, overstimulation of the nipple area and the wrong massage technique can trigger the release of the hormone oxytocin, which can cause uterine contractions. This is risky in high-risk pregnancies or before the safe time of delivery. Therefore, before performing a breast massage, you should consult a competent health professional regarding the proper breast massage procedure or technique. It is very important to avoid the possibility of premature contractions of the mother in the late trimester.¹⁹

Oxytocin massage is also a method that is widely discussed in the literature as a beneficial intervention. Oxytocin massage aims to stimulate the mammary glands and increase the release of the hormone oxytocin, which plays an important role in the breastfeeding process. By focusing on this technique, the mother may experience an improvement in the smoothness of milk production, which in turn may improve the quality of exclusive breastmilk that the infant receives.²⁰

Conclusion

Based on the results of data presentation and discussion in this study, it can be concluded that breast massage training affects increasing mothers' knowledge and improving their skills in performing breast massage. Before receiving breast massage, the mothers were unable to secrete colostrum. However, after breast massage was performed, the mothers were able to secrete colostrum.

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References

1. Doko TM, Aristiati K, Hadisaputro S. Pengaruh Pijat Oksitosin oleh Suami terhadap Peningkatan Produksi Asi pada Ibu Nifas. *Jurnal Keperawatan Silampari*. 2019 May 16;2(2):66–86.
2. Kementerian Kesehatan Republik Indonesia. Laporan Akuntabilitas Kinerja Instansi Pemerintah Tahun 2022. 2022. 31–32 p.
3. Namira ATP. Hubungan Pemberian ASI Eksklusif Terhadap Perkembangan Motorik Halus pada Bayi Usia 6-12 Bulan di Kabupaten Pinrang Tahun 2021. *Fakultas Kedokteran dan Ilmu Kesehatan*. 2021;1–103.
4. Nurliza, Diana MI. Pengaruh Pijat Oksitosin Dan Breast Care Terhadap Produksi ASI Ibu Nifas Di Klinik Utama Arpasar Rebo. *Jurnal Ilmiah Kesehatan Dan Kebidanan*. 2020;1–12.

5. Nur Soleha S, Sucipto E, Izah N, III Kebidanan D, Harapan Bersama P. Pengaruh Perawatan Payudara Terhadap Produksi ASI Ibu Nifas Mo. *Jurnal Ilmiah Kebidanan*.
6. Sari VPU, Syahda S. Pengaruh Pijat Oketani Terhadap Produksi Asi Pada Ibu Nifas Di Wilayah Kerja Puskesmas Bangkinang Kota. *Jurna; Doppler*. 2020;4(2).
7. Sari SIP, Harahap JR, Helina S. Pelatihan Pijat Laktasi Untuk Kader Kesehatan. 2021. 1–30 p.
8. Dinengsih S. Pengaruh Kombinasi Pijat Woolwich dan Pijat Oksitoksin Terhadap Produksi ASI pada Ibu Post Partum. *Journal for Quality in Women's Health*. 2020 Sep 1;3(2):133–9.
9. Fatimah S, Rosdiana, Nurayuda, Surti A. Pengaruh Metode Pijat Woolwich Dan Akupuntur Titik Gb 21 Terhadap Produksi ASI. *Journal Health and Science*. 2022;6(1).
10. Zulfiana E, Rahmanindar N, Hidayah SN, Safitri D. Peningkatan Pengetahuan Ibu Nifas tentang Terapy Komplementer Pijat Laktasi di Margadana. *ARDHI : Jurnal Pengabdian Dalam Negri*. 2024 Feb 17;2(1):155–7.
11. Zuraidah, Aprilyadi N, Soewito B, Juartika W. Pelatihan hypnobreastfeeding pada tenaga kesehatan untuk meningkatkan produksi ASI pada ibu menyusui. *Penamas: Journal of Community Service*. 2024 May 16;4(1):81–9.
12. Lestariningsih S, Lestari GI, Khoiriyah D, Devianti Y, Putri PD, Yuhana L. Pijat oksitosin untuk mengatasi ASI tidak lancar pada ibu menyusui di Puskesmas Tejo Agung. *Penelitian dan Pengabdian Inovatif pada mAsa PAndemi Covid-19*. 2021;978–623.
13. Rihi P, Pella YH, Lagut YN. Edukasi Perawatan Payudara Pada Ibu Hamil dan Nifas di Posyandu Kenari Naikoten 1. *Nanggroe : Jurnal Pengabdian Cendikia*. 2024;3(4):183–6.
14. Mulazimah, Nurahmawati D, Kholis MN, Noeraini AR, Junita ME, Klau AS. Peningkatan Produksi Asi Ibu Menyusui Melalui Breast Care Di Puskesmas Perawatan Ngletih Kota Kediri. *Kontribusi: Jurnal Penelitian dan Pengabdian Kepada Masyarakat*. 2023 May 12;3(2):88–97.
15. Sembiring DB. Efektifitas Perawatan Payudara Dengan Tehnik Pijat Oketani Terhadap Kelancaran Produksi ASI. *Journal of Health and Medical Science*. 2023;3(1):21–8.
16. Ningsih DA, Masyayih WA, Indriani T, Susiana S, Kholifah UN, Romlah S. Pengaruh video pijat endhoprin terhadap kelancaran ASI pada ibu menyusui. *JOMIS (Journal of Midwifery Science)*. 2023 Jan 28;7(1):59–68.
17. Imbar H, Montol AB, Losu FN, Pasambo Y, Momongan NR. Pelatihan Mekanisme Konseling Menyusui Eksklusif Pada Kader Kesehatan Dan Tokoh Agama. *Jurnal Pengabdian kepada Masyarakat Nusantara* . 2023;4(3).
18. Istiananingsih Y, Rahmaika D, Romdhona N, Riffeby SA, Putri Y. Buku saku pijat laktasi. Vol. 1. 2023. 6–9 p.
19. Jahriani N. Pengaruh Pijat Laktasi Terhadap Produksi ASI Pada Ibu Menyusui Di Kelurahan Sendang Sari Kabupaten Asahan Tahun 2019. *Excellent Midwifery Journal*. 2019;2(2):14–20.
20. Juwariah, Farah YD, Mayasari AT, Abdullah. Pengaruh pijat oksitosin terhadap peningkatan produksi ASI ibu postpartum. *Wellness and healthy magazine*. 2020;2(2):269–75.

Case Report

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Alcohol-Associated Decompensated Cirrhosis with Ascites and Suspected Hepatic Encephalopathy: A Case Report

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ABSTRACT

Introduction: Alcohol-associated cirrhosis is a preventable cause of advanced liver disease, yet it is frequently first recognized after decompensation. This case underscores the diagnostic value of integrating clinical decompensating features with non-invasive fibrosis indices and ultrasonography in a resource-limited setting.

Case Summary: A 51-year-old man with a 20-year history of daily alcohol intake presented with progressive abdominal distension, bilateral leg edema, right hypochondrial pain, nausea, jaundice, weight loss, and recent behavioral change. He had previous hematemesis and melena but had declined esophagogastroduodenoscopy. Examination revealed pallor, scleral icterus, ascites, right hypochondrial tenderness, and peripheral edema. Investigations showed anemia, thrombocytopenia, AST-predominant transaminitis, hypoalbuminemia, mild hyponatremia, and non-reactive HBsAg. APRI and FIB-4 were markedly elevated, and ultrasonography demonstrated a shrunken, coarse, irregular liver with ascites, supporting a diagnosis of presumed alcohol-associated decompensated cirrhosis. Behavioral changes without impaired consciousness were clinically suggestive of early hepatic encephalopathy; however, covert hepatic encephalopathy could not be formally confirmed because psychometric testing was not available.

Discussion: Ascites, jaundice, cytopenia, hypoalbuminemia, and neuropsychiatric change indicated advanced decompensation, while suspected portal hypertension remained incompletely characterized because endoscopy was unavailable. Management included dietary sodium and fluid restriction, nutritional support, large-volume paracentesis, albumin infusion, empiric antibiotic therapy, acid suppression, ursodeoxycholic acid, diuretic therapy, lactulose, and a non-selective beta-blocker.

Conclusion: This case emphasizes early alcohol-use assessment, abstinence-centered care, timely endoscopic risk stratification, and complication-directed management to reduce preventable deterioration in alcohol-associated decompensated cirrhosis.

Keywords: Alcohol-associated liver disease; decompensated cirrhosis; ascites; hepatic encephalopathy; case report



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Introduction

Cirrhosis represents the advanced stage of chronic liver injury, characterized by progressive fibrosis, regenerative nodules, distortion of hepatic architecture, portal hypertension, and gradual loss of hepatocellular function¹⁻³. Although patients may remain clinically silent during the compensated phase, the onset of ascites, jaundice, variceal bleeding, infection, renal dysfunction, or hepatic encephalopathy marks the transition to decompensated disease and is associated with substantially poorer outcomes⁴. Recent Global Burden of Disease estimates reported approximately 58.4 million incident cases of liver cirrhosis in 2021, increasing from 36.9 million in 1990, while deaths related to cirrhosis and other chronic liver diseases exceeded 1.4 million in 2021^{5,6}.

Alcohol-associated liver disease is one of the most important preventable causes of cirrhosis. Sustained alcohol exposure may produce a continuum of hepatic injury, ranging from steatosis and steatohepatitis to advanced fibrosis and decompensated cirrhosis⁷⁻¹⁰. Its burden is clinically relevant because many patients are diagnosed late, when complications such as ascites, jaundice, anemia, thrombocytopenia, malnutrition, and neuropsychiatric manifestations have already developed. Contemporary estimates show that alcohol-associated liver disease affects approximately 3.5% of the general population and is substantially more frequent among hazardous drinkers and individuals with alcohol use disorder¹¹.

In Indonesia, cirrhosis remains an important clinical problem, although national population-based data are limited. The Indonesian clinical practice guideline for adult liver cirrhosis notes a substantial national burden of cirrhosis-related mortality, with Social Security Agency on Health (BPJS Kesehatan) data documenting 2,159 deaths attributed collectively to cirrhosis and liver cancer in 2022¹². This combined figure does not represent cirrhosis-specific mortality. These data highlight the need for early recognition of advanced liver disease, especially in patients with long-standing risk factors such as chronic alcohol consumption.

Diagnosis of decompensated cirrhosis requires integration of clinical findings, laboratory abnormalities, non-invasive fibrosis indices, and imaging features¹³. In settings where advanced diagnostic procedures are not immediately obtained, findings such as ascites, jaundice, thrombocytopenia, hypoalbuminemia, altered behavior, APRI, FIB-4, and ultrasonography may provide a practical framework for recognizing advanced liver disease and initiating early complication-directed management¹⁴. We report a case of presumed alcohol-associated decompensated cirrhosis in a 51-year-old man in whom diagnosis and initial management were established primarily from clinical assessment, routinely available laboratory investigations, and abdominal ultrasonography. The educational value of this case lies in demonstrating a pragmatic approach to recognizing and managing decompensated cirrhosis when diagnostic evaluation is incomplete and more definitive assessment, particularly endoscopic evaluation of portal hypertension, has not yet been obtained.

Case Report

A 51-year-old married man presented to the emergency department with progressive abdominal distension for approximately one month, accompanied by bilateral lower-limb swelling. He also reported right-sided abdominal pain for five days, nausea, progressive yellow discoloration of the eyes and skin for one week, and unintentional weight loss over the preceding five months. During the same week, his family noticed behavioral changes, including reduced communication and irritability, raising suspicion for covert hepatic encephalopathy. He had a history of hematemesis and melena in the previous year but declined esophagogastroduodenoscopy and further inpatient evaluation at that time. He had consumed alcohol daily for approximately 20 years, although the exact amount could not be quantified, and had a 20-pack-year smoking history.

On admission, the patient was conscious and hemodynamically stable, with a blood pressure of 100/55 mmHg, pulse rate of 78 beats/minute, respiratory rate of 20 breaths/minute, temperature of 36.4°C, and oxygen saturation of 100% on room air. Relevant physical findings included pale conjunctivae, scleral icterus, a protuberant abdomen with positive shifting dullness, tenderness over the right hypochondriac region, and bilateral lower-limb edema. No clinically apparent hepatosplenomegaly was detected. Peripheral stigmata of chronic liver disease, including palmar erythema, spider angioma, and gynecomastia, were not observed, while testicular atrophy was not assessed. Tremor and asterixis were not documented. The reported reduction in communication and irritability were considered clinically suggestive of early hepatic encephalopathy; however, these findings were nonspecific, and covert hepatic encephalopathy could not be formally confirmed because psychometric testing was not available.

Laboratory evaluation showed bicytopenia characterized by anemia and thrombocytopenia, with hemoglobin 11.44 g/dL, hematocrit 35.8%, erythrocytes $4.302 \times 10^6/\mu\text{L}$, platelets $80 \times 10^3/\mu\text{L}$, and a leukocyte count of $8.26 \times 10^3/\mu\text{L}$. Liver biochemistry demonstrated AST-predominant transaminitis, with AST 203.70 U/L and ALT 54.00 U/L. Serum albumin was low, with recorded values of 2.1 and 2.0 g/dL during hospitalization; the exact timing of the repeat measurement relative to intravenous albumin administration was not documented in the available record. Renal function was preserved, with BUN 7.14 mg/dL and creatinine 0.645 mg/dL. Mild hyponatremia was present, with sodium 134.80 mmol/L. HBsAg was non-reactive. Urinalysis showed protein 2+, bilirubin 2+, urobilinogen 2+, leukocytes 2+, and bacteriuria. Further etiological evaluation, including testing for hepatitis C and other causes of chronic liver disease, could not be completed because of facility and financial limitations. Moreover, serum bilirubin and coagulation parameters, including PT/INR, were not available during this admission; therefore, disease severity could not be fully assessed using the Child–Pugh and MELD-Na scores.

Non-invasive fibrosis assessment strongly supported cirrhosis, with an AST-to-platelet ratio index of 7.3 and a Fibrosis-4 index of 17.67. Abdominal ultrasonography demonstrated a shrunken liver with coarse

increased echotexture, irregular surface, and ascites (Figure 1). The working diagnosis of presumed alcohol-associated decompensated cirrhosis was made based on the integration of long-term alcohol exposure, ascites, jaundice, thrombocytopenia, hypoalbuminemia, AST-dominant aminotransferase elevation, high APRI and FIB-4 scores, and cirrhotic morphology on ultrasonography. The main clinical manifestations were ascites, jaundice, anemia, thrombocytopenia, lower-limb edema, and behavioral change suggestive of covert hepatic encephalopathy. Portal hypertension was suspected from the presence of ascites and thrombocytopenia, although varices were not confirmed because esophagogastroduodenoscopy (EGD) had not been performed as the patient had previously refused it.

The initial diagnostic approach therefore relied on investigations available in the documented clinical work-up, including complete blood count, liver aminotransferases, serum albumin, renal function, serum sodium, HBsAg, urinalysis, non-invasive fibrosis indices, and abdominal ultrasonography. These findings were sufficient to support advanced chronic liver disease with clinical decompensation and to guide initial treatment. Endoscopic assessment of portal hypertension was not obtained because the patient had previously declined EGD, and other investigations not documented in the available work-up were not used to establish the initial diagnosis.



Figure 1. Abdominal Ultrasonography Showing Cirrhotic Liver Morphology with Ascites. The liver appears shrunken with coarse increased echotexture and an irregular surface, accompanied by ascites, consistent with hepatic cirrhosis.

Management focused on controlling decompensated cirrhosis and its associated complications. The patient received dietary sodium restriction as part of ascites management, together with a low-fat, high-protein diet. Therapeutic paracentesis was performed with removal of 6 L of ascitic fluid. The patient also received 100 mL of 25% intravenous albumin during hospitalization. The serum albumin level was 2.0 g/dL before albumin

administration and increased to 2.1 g/dL following the infusion. Other pharmacological treatment included intravenous cefuroxime 1 g three times daily as empiric antibiotic therapy for suspected infection, intravenous metamizole 1 g three times daily, intravenous pantoprazole 40 mg once daily (as acid-suppressive therapy in the context of gastrointestinal symptoms and the patient's previous history of hematemesis and melena), intravenous furosemide 40 mg once daily, oral spironolactone 100 mg once daily, oral lactulose 5 mL three times daily, oral propranolol 20 mg twice daily, and oral ursodeoxycholic acid 250 mg twice daily.

During the five-day hospitalization, no active gastrointestinal bleeding, renal failure, or overt deterioration in consciousness was documented. Clinical improvement was observed, with reduced abdominal distension and lower-limb edema, improvement in abdominal pain, and better communication and behavior. Renal function remained preserved, with adequate urine output, and no significant treatment-related adverse events were documented. The patient was considered clinically stable for discharge and was discharged with dietary advice, oral medications, counseling regarding alcohol abstinence, and scheduled internal medicine follow-up. However, he did not return for the scheduled follow-up; therefore, longer-term clinical outcomes and completion of further diagnostic evaluation could not be assessed.

Discussion

This case illustrates presumed alcohol-associated decompensated cirrhosis presenting with ascites, jaundice, anemia, thrombocytopenia, hypoalbuminemia, and behavioral changes suggestive of covert hepatic encephalopathy. The diagnosis was supported by a long history of daily alcohol consumption, AST-predominant aminotransferase elevation, thrombocytopenia, hypoalbuminemia, markedly elevated APRI and FIB-4 scores, and ultrasonographic evidence of a shrunken liver with coarse echotexture, irregular surface, and ascites. These findings are consistent with advanced chronic liver disease complicated by clinical decompensation.

The bicytopenia in this patient consisted of anemia and thrombocytopenia with a preserved leukocyte count. These hematologic abnormalities were likely multifactorial, with possible contributions from portal hypertension and hypersplenism, nutritional deficiency, alcohol-associated bone marrow suppression, and the previous history of gastrointestinal bleeding. Further hematologic evaluation was not available to determine the relative contribution of each mechanism.

The clinical importance of this case lies in the late recognition of alcohol-associated cirrhosis after the development of multiple decompensating features. Cirrhosis may remain asymptomatic during the compensated phase, whereas decompensation is commonly marked by ascites, variceal bleeding, jaundice, or hepatic encephalopathy and is associated with more rapid progression toward death or liver transplantation¹⁵. In this patient, ascites was the dominant presentation, accompanied by jaundice, peripheral edema, hypoalbuminemia, thrombocytopenia, and neuropsychiatric change. This constellation supports a transition

from chronic compensated liver injury to clinically evident decompensated cirrhosis.

Alcohol-associated liver disease was considered the most likely etiology in this patient. He had consumed alcohol daily for approximately 20 years; however, the exact amount of alcohol intake could not be reliably quantified. The available etiological evaluation was limited, with HBsAg being non-reactive, while hepatitis C and other causes of chronic liver disease could not be fully excluded because of facility and financial limitations. Therefore, considering the long-term alcohol exposure together with the clinical, biochemical, and ultrasonographic findings, the diagnosis was regarded as presumed alcohol-associated decompensated cirrhosis.

Sustained alcohol exposure can progress from steatosis and steatohepatitis to fibrosis and cirrhosis, and long-standing intake of more than 40 g/day has been associated with cirrhosis in a substantial proportion of exposed individuals^{9,16}. Recent epidemiological data also show that alcohol-associated liver disease remains a major global problem, with an estimated prevalence of 3.5% in the general population, 26.0% among hazardous drinkers, and 55.1% among individuals with alcohol use disorder¹¹. In the present case, the negative HBsAg result and the absence of stronger alternative etiologies in the available work-up further supported alcohol-associated liver disease as the leading cause.

Ascites and thrombocytopenia suggested clinically significant portal hypertension, although this could not be fully characterized because EGD was not performed. This limitation is clinically relevant because the patient had a prior history of hematemesis and melena, which raises concern for previous variceal bleeding. Endoscopic evaluation would have been important for detecting gastroesophageal varices and guiding primary or secondary prophylaxis. Current guidance emphasizes complication-directed management in decompensated cirrhosis, including ascites control, infection prevention, evaluation for varices, and treatment of hepatic encephalopathy when clinically indicated^{1,2,17}.

An important practical aspect of this case was that the initial diagnosis did not depend on liver biopsy, transient elastography, or endoscopic confirmation. Instead, the clinical diagnosis was established by combining a long history of alcohol exposure with recognizable decompensating features, routine laboratory abnormalities, markedly elevated APRI and FIB-4 values, and ultrasonographic evidence of cirrhotic morphology. This approach is particularly relevant in settings where the diagnostic work-up is incomplete or where advanced investigations cannot be obtained immediately. In such circumstances, primary and general-care physicians should recognize that the presence of ascites, jaundice, thrombocytopenia, hypoalbuminemia, and compatible ultrasonographic findings may be sufficient to identify probable decompensated cirrhosis, initiate appropriate supportive and complication-directed treatment, and arrange referral or further evaluation for portal hypertension and other complications.

The suspected hepatic encephalopathy should be interpreted cautiously. The patient's family reported reduced communication and irritability, while he remained *compos mentis* and asterixis was not documented.

These behavioral changes were clinically suggestive of early hepatic encephalopathy but were nonspecific. Psychometric testing was not available; therefore, covert hepatic encephalopathy could not be formally confirmed. Other potential contributors to behavioral change, including infection, electrolyte disturbance, gastrointestinal bleeding, medication-related effects, and alcohol withdrawal, should also be considered. In this patient, mild hyponatremia and suspected infection represented possible alternative or precipitating factors, while no active gastrointestinal bleeding was documented during hospitalization. This distinction is important because hepatic encephalopathy spans a wide neuropsychiatric spectrum and requires careful clinical correlation and exclusion of alternative causes of altered mental status ¹⁸.

Management in this case included dietary salt and fluid restriction, nutritional support, therapeutic paracentesis, albumin infusion, empiric antibiotic therapy, acid suppression, diuretic therapy with furosemide and spironolactone, lactulose, non-selective beta-blocker therapy with propranolol, and ursodeoxycholic acid. In terms of the use of antibiotics, spontaneous bacterial peritonitis could not be microbiologically or cytologically confirmed because ascitic fluid analysis was unavailable; therefore, antibiotic therapy was administered empirically for suspected infection.

For alcohol-associated cirrhosis, sustained abstinence remains a central disease-modifying intervention, with recent meta-analytic evidence showing that abstinence is associated with improved overall survival ¹⁹. More importantly, this case demonstrates that early recognition and initial management of advanced liver disease can be guided by careful clinical assessment and a limited but appropriately selected diagnostic work-up, while definitive evaluation of portal hypertension and other complications should be pursued when feasible.

This case has several limitations related to the incomplete diagnostic work-up in a resource-limited clinical setting. As detailed in the Case Report, incomplete laboratory data precluded formal disease-severity scoring. Comprehensive etiological evaluation, including testing for hepatitis C and other causes of chronic liver disease, was also limited. Ascitic fluid analysis was unavailable; therefore, spontaneous bacterial peritonitis could not be confirmed. In addition, psychometric testing was not available to formally confirm covert hepatic encephalopathy. Endoscopic evaluation for portal hypertension and gastroesophageal varices was not completed because the patient had previously declined esophagogastroduodenoscopy. Despite these limitations, the integration of clinical findings, available laboratory results, non-invasive fibrosis indices, and ultrasonographic features strongly supported the working diagnosis of presumed alcohol-associated decompensated cirrhosis and allowed initial complication-directed management. Long-term outcome assessment was also limited because the patient did not return for scheduled follow-up after discharge.

Conclusion

This case highlights the practical importance of recognizing a late presentation of presumed alcohol-associated decompensated cirrhosis using clinical findings, routinely available laboratory tests, non-invasive

fibrosis indices, and ultrasonography when the diagnostic work-up is incomplete. In this patient, ascites, jaundice, thrombocytopenia, hypoalbuminemia, AST-predominant transaminitis, markedly elevated APRI and FIB-4 scores, and cirrhotic morphology on ultrasonography supported the working diagnosis and initial management despite the absence of endoscopic characterization of portal hypertension. Behavioral changes were clinically suggestive of early hepatic encephalopathy, although covert hepatic encephalopathy could not be formally confirmed because psychometric testing was unavailable. The main practical lesson is that clinicians should not delay recognition and complication-directed management of probable decompensated cirrhosis while awaiting more advanced investigations. Alcohol abstinence, nutritional optimization, control of decompensating events, appropriate referral for endoscopic assessment, and close follow-up remain essential to reduce further deterioration.

Patient Consent

Written informed consent for publication of this case report was obtained from the patient.

Conflicts of Interest

The authors declare that they have no conflicts of interest related to the publication of this case report.

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References

1. Tapper EB, Parikh ND. Diagnosis and Management of Cirrhosis and Its Complications. *JAMA*. 2023;329(18):1589. doi: 10.1001/jama.2023.5997
2. Fadlallah H, El Masri D, Bahmad HF, Abou-Kheir W, El Masri J. Update on the Complications and Management of Liver Cirrhosis. *Medical Sciences*. 2025;13(1):13. doi: 10.3390/medsci13010013
3. Del Cioppo S, Faccioli J, Ridola L. Hepatic cirrhosis and decompensation: Key indicators for predicting mortality risk. *World J Hepatol*. 2025;17(3). doi: 10.4254/wjh.v17.i3.104580
4. Jagdish RK, Roy A, Kumar K, Premkumar M, Sharma M, Rao PN, et al. Pathophysiology and management of

- liver cirrhosis: from portal hypertension to acute-on-chronic liver failure. *Front Med (Lausanne)*. 2023;10. doi: 10.3389/fmed.2023.1060073
5. Sepanlou SG, Safiri S, Bisignano C, Ikuta KS, Merat S, Saberifiroozi M, et al. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol*. 2020;5(3):245–66. doi: 10.1016/S2468-1253(19)30349-8
 6. Luo X, He Y, Jiang Z, Liao J. Global burden of liver cirrhosis: trends from 1990–2021 and projections to 2060. *J Health Popul Nutr*. 2025;44(1):370. doi: 10.1186/s41043-025-01109-5
 7. Lin H-M, Zhang J-R, Li M-X, Hou H, Wang H, Huang Y. Cigarette smoking and alcohol-related liver disease. *Liver Res*. 2024;8(4):237–45. doi: 10.1016/j.livres.2024.12.002
 8. Ha Y, Jeong I, Kim TH. Alcohol-Related Liver Disease: An Overview on Pathophysiology, Diagnosis and Therapeutic Perspectives. *Biomedicines*. 2022;10(10):2530. doi: 10.3390/biomedicines10102530
 9. Mackowiak B, Fu Y, Maccioni L, Gao B. Alcohol-associated liver disease. *Journal of Clinical Investigation*. 2024;134(3). doi: 10.1172/JCI1176345
 10. Liu S-Y, Tsai I-T, Hsu Y-C. Alcohol-Related Liver Disease: Basic Mechanisms and Clinical Perspectives. *Int J Mol Sci*. 2021;22(10):5170. doi: 10.3390/ijms22105170
 11. Åberg F, Jiang ZG, Cortez-Pinto H, Männistö V. Alcohol-associated liver disease—Global epidemiology. *Hepatology*. 2024;80(6):1307–22. doi: 10.1097/HEP.0000000000000899
 12. Kementerian Kesehatan Republik Indonesia. Pedoman Nasional Pelayanan Klinis Tata Laksana Sirosis Hati Pada Dewasa. <https://www.kemkes.go.id/id/pedoman-nasional-pelayanan-klinis-tata-laksana-sirosis-hati-pada-dewasa>. 2025. [accessed 29 Apr 2026] Available from: <https://www.kemkes.go.id/id/pedoman-nasional-pelayanan-klinis-tata-laksana-sirosis-hati-pada-dewasa>
 13. Engelmann C, Clària J, Szabo G, Bosch J, Bernardi M. Pathophysiology of decompensated cirrhosis: Portal hypertension, circulatory dysfunction, inflammation, metabolism and mitochondrial dysfunction. *J Hepatol*. 2021;75:S49–66. [accessed 29 Apr 2026] Available from: <https://www.journal-of-hepatology.eu/action/showFullText?pii=S0168827821000027>
 14. Nsumbu J-B, Makulo J-R, Mutombo Tshiswaka T, Kisoka Lusunsi C, Nlombi Mbendi C. Performance of APRI and FIB-4 Scores Compared to FibroScan: A Cross-Sectional Study in a Black Sub-Saharan African Population. *Hepat Med*. 2025;Volume 17:27–37. doi: 10.2147/HMER.S533064
 15. Kumar R, Kumar S, Prakash SS. Compensated liver cirrhosis: Natural course and disease-modifying strategies. *World J Methodol*. 2023;13(4):179–93. doi: 10.5662/wjm.v13.i4.179
 16. Huang DQ, Mathurin P, Cortez-Pinto H, Loomba R. Global epidemiology of alcohol-associated cirrhosis and HCC: trends, projections and risk factors. *Nat Rev Gastroenterol Hepatol*. 2023;20(1):37–49. doi: 10.1038/s41575-022-00688-6
 17. Jakab SS, Garcia-Tsao G. Evaluation and Management of Esophageal and Gastric Varices in Patients with Cirrhosis. *Clin Liver Dis*. 2020;24(3):335–50. doi: 10.1016/j.cld.2020.04.011
 18. Sharma K, Akre S, Chakole S, Wanjari MB. Hepatic Encephalopathy and Treatment Modalities: A Review Article. *Cureus*. 2022 Aug 14;14(8):e28016. doi: 10.7759/cureus.28016
 19. Lim WH, Tay P, Ng CH, Tan DJH, Ong C, Koh JH, et al. Meta-analysis: Prevalence and impact of alcohol abstinence in alcohol-associated cirrhosis. *Aliment Pharmacol Ther*. 2024;59(6):730–41. doi: 10.1111/apt.17888

Review article

Open Access

Central Post-Stroke Pain: Evidence-Based Rehabilitation Strategies for Neuropathic Pain Management

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ABSTRACT

Introduction: Central Post-Stroke Pain (CPSP) is a common and challenging condition that affects 8-10% of stroke survivors, significantly impacting their quality of life and functional recovery. Despite its prevalence, effective management remains complex and multifaceted.

Contents: This review explores rehabilitation strategies for CPSP, emphasizing the role of both pharmacological and non-pharmacological interventions. Exercise therapy, including strength training, aerobic conditioning, and flexibility exercises, plays a pivotal role in alleviating pain, enhancing neural plasticity, and improving functional outcomes. Additionally, physical modalities such as transcranial magnetic stimulation (rTMS) and acupuncture, along with psychological approaches like Cognitive Behavioral Therapy (CBT) and Acceptance and Commitment Therapy (ACT), address the emotional and cognitive components of CPSP.

Conclusion: A multidisciplinary, patient-centered approach integrating exercise, physical modalities, and psychosocial support is essential for optimizing CPSP management. Further research is needed to refine and standardize rehabilitation protocols to achieve long-term pain relief and improved recovery outcomes for stroke survivors.

Keywords: Exercise therapy; pain; transcranial magnetic stimulation



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Introduction

Stroke, a critical health emergency, remains a significant global burden. According to the World Health Organization (WHO), stroke is the second leading cause of death worldwide and the primary cause of long-term disability. Each year, over 13 million new stroke cases are reported, posing a serious challenge in providing effective and holistic care for stroke survivors (WHO, 2018). Amidst the evolving landscape of post-stroke care, one aspect that is often overlooked yet has a profound impact is central post-stroke pain (CPSP).

Epidemiological data reveal that CPSP, a chronic pain condition that emerges following a stroke, affects approximately 8-10% of the stroke population ¹. This high prevalence underscores the importance of understanding and effectively managing post-stroke pain, given its detrimental effects on quality of life, physical function, and psychological well-being.

Given these striking epidemiological findings, this review aims to explore in-depth the rehabilitation strategies for managing CPSP. To begin, it is essential to recognize that CPSP arises as a result of damage to the central nervous system, primarily caused by stroke. Stroke itself can result from various factors, including ruptured or blocked blood vessels, leading to insufficient blood supply to the brain. Advances in understanding the pathophysiology of stroke have provided further insights into the prevalence and risk factors associated with CPSP.

In the context of rehabilitation management, clinicians must prioritize accurate evaluation and diagnosis. Comprehensive clinical and neurological examinations are crucial to assess the extent of central nervous system damage and its impact on post-stroke pain. Additionally, advanced diagnostic tools, such as neuroimaging, offer deeper insights into the structural and functional changes in the brains of affected individuals. Rehabilitation approaches for CPSP extend beyond pharmacological management. Non-pharmacological therapies, including physiotherapy, occupational therapy, and cognitive therapy, play a pivotal role in restoring motor function, mitigating psychological impacts, and enhancing overall quality of life. Recent research also highlights the critical role of neuroplasticity in supporting rehabilitation and the brain's adaptation to injury.

Nevertheless, pharmacological treatment remains an integral component of CPSP management. Analgesics, antidepressants, and anticonvulsants are commonly used to address neuropathic pain and associated psychological symptoms. However, the choice of medication and dosage must be tailored to individual patient characteristics, with careful monitoring for potential side effects. In this context, a holistic approach that incorporates psychosocial support is equally indispensable. Family support, psychological counseling, and participation in support groups can provide the understanding, emotional reinforcement, and motivation necessary for a more effective recovery journey.

This review emphasizes the importance of a multidisciplinary and patient-centered approach to managing CPSP, integrating both pharmacological and non-pharmacological strategies to optimize outcomes

for stroke survivors.

Methods

This manuscript is a narrative review that summarizes current evidence regarding rehabilitation strategies for Central Post-Stroke Pain (CPSP). A literature search was conducted using PubMed, Scopus, ScienceDirect, and Google Scholar databases for articles published between 2009 and 2025. The search terms included "Central Post-Stroke Pain", "Stroke Rehabilitation", "Exercise Therapy", and "Neuropathic Pain". Original studies, randomized controlled trials, systematic reviews, meta-analyses, and clinical practice guidelines focusing on rehabilitation interventions for CPSP were included. Studies unrelated to rehabilitation management or addressing peripheral neuropathic pain were excluded. The selected literature was narratively synthesized according to rehabilitation modalities and their clinical applications.

Pain Physiology

Pain is a complex physiological process that serves as a protective mechanism, alerting the body to potential harm and enabling appropriate responses. The mechanism of pain involves three primary steps: (1) the detection of harmful stimuli by sensory receptors (transduction), (2) the transmission of electrical signals through neural pathways, and (3) the modulation of pain intensity at various levels of the nervous system. These processes collectively result in the perception of pain following the initiation and cessation of harmful stimuli.²

Nociceptive transduction is the process through which harmful stimuli are converted into electrical signals in neurons, starting with the transformation of physical stimuli into chemical signals. These signals are then turned into electrical impulses in sensory neurons, with further conversion into chemical messengers at the synaptic level. This process, essential for the body's perception of touch and pain, occurs when the somatosensory system opens ion channels in response to physical stimuli, allowing electrochemical signals to be transmitted to higher neural centers. Sensory coding plays a key role in translating receptor signals into recognizable sensations by encoding four primary attributes of a stimulus: modality, location, intensity, and duration.³ This allows the body to interpret sensory inputs and perceive the external environment. Neurons, which consist of soma, axons, and dendrites, form networks that transmit signals through synapses, either exciting or inhibiting neural activity depending on the chemical messengers involved. When neurons receive signals, they generate action potentials that travel along axons and activate synapses, transmitting messages to other neurons and facilitating communication between different regions of the brain and spinal cord.⁴

The somatosensory system detects a wide range of mechanical stimuli, from light touch to bladder distension, with mechanosensitive nerve fibers being crucial in detecting these stimuli. Nociceptors convert

harmful stimuli into electrical signals, triggering inflammatory responses and sensitization, which heighten swelling and pain in the affected area. Transmission of nociceptive signals occurs when primary nociceptors send signals to second-order neurons in the dorsal horn of the spinal cord, carried by A δ and C fibers.⁵ These fibers synapse with second-order neurons in laminae II and V, where nociceptive-specific (NS) neurons in lamina I respond to C fiber inputs and wide dynamic range (WDR) neurons in lamina V process a variety of stimuli. Pain modulation, which controls the transmission of pain signals, occurs at the brain, brainstem, and spinal cord levels, involving inhibitory control from higher centers and natural opioid and cannabinoid systems, among others. Finally, pain perception is shaped by the activation of a distributed cortical network known as the pain neuromatrix, with key regions such as the somatosensory cortex, insula, anterior cingulate cortex, prefrontal cortex, and amygdala working together to form the overall experience of pain.²

Sensitization Theory

The sensitization theory of pain explains that high-intensity, noxious stimuli, even if brief and without tissue damage, can activate nociceptors and induce pain. Small-diameter nerve fibers with high thresholds activate nociceptors, causing transient pain. In contrast, larger-diameter fibers with lower thresholds transmit sensations such as pressure and touch. These fibers communicate with other neurons in the spinal cord.⁵

Tissue injury and the release of inflammatory mediators increase nociceptor sensitivity, leading to repeated activation. This sensitization involves inflammatory mediators, which heighten nociceptor responsiveness and result in primary hyperalgesia—an increased response to both painful and non-painful stimuli.⁵

Persistent pain signals can enhance the sensitivity of spinal cord neurons, a phenomenon known as wind-up. This leads to secondary hyperalgesia and the spread of pain to surrounding areas. Inhibitory interneurons and descending inhibitory pathways help mitigate this sensitization. Analgesics and pain management strategies also play a role in reducing sensitization.⁵

Inflammatory mediators and pro-inflammatory cytokines, such as interleukin (IL)-1 β and IL-6, exacerbate pain and inflammation. Effective treatment can reduce the levels of these cytokines. Genetic factors also influence individual responses to postoperative pain.⁵

Central Pain Syndrome Post Stroke

Central Pain Syndrome (CPS), initially introduced by Edinger in 1891, was notably elaborated by Déjerine and Roussy in their seminal 1906 work "Le syndrome thalamique".⁶ They described severe, persistent, paroxysmal pain occurring on the hemiplegic side, unresponsive to analgesics, linked primarily to lesions in

the optic thalamus and adjacent posterior internal capsule. Subsequent studies, notably by Head and Holmes (1911) and Riddoch (1938), expanded understanding, revealing that central pain could result from lesions beyond the thalamus, thus leading to the contemporary preference for the term Central Post-Stroke Pain (CPSP).⁷

CPSP, categorized under central neuropathic pain disorders, arises directly from lesions or dysfunctions within the central nervous system (CNS).⁸ Diagnosing CPSP remains challenging due to overlapping symptoms with other pain types post-stroke, including headaches, musculoskeletal pain, hemiplegic shoulder pain, and spasticity-related pain.⁹ Current definitions emphasize the presence of neuropathic pain characteristics, sensory disturbances, confirmed CNS lesions, and the exclusion of other potential pain etiologies¹⁰

Epidemiologically, CPSP affects approximately 1% to 12% of stroke survivors, with higher prevalence (up to 18%) among those experiencing sensory deficits.¹¹ CPSP symptoms typically manifest as spontaneous dysesthesias or stimulus-triggered pain described as burning, freezing, stabbing, or squeezing sensations. Allodynia and hyperalgesia are also frequently reported, significantly impacting quality of life.¹

Clinically, CPSP can result from lesions at various CNS locations, including the thalamus, lenticulocapsular region, cerebral cortex, pons, and medulla.¹² Thalamic lesions remain most commonly associated with CPSP, specifically involving the ventral posterolateral nucleus.¹³ However, cortical, lenticulocapsular, pontine, and medullary strokes also contribute uniquely to CPSP presentations, influenced by lesion location and associated sensory pathway disruptions.¹²

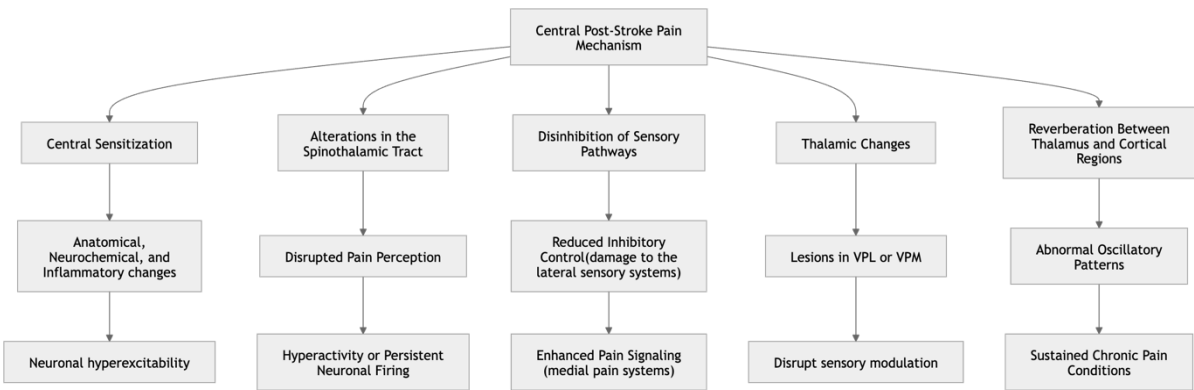


Figure 1 Mechanism of Central Post-Stroke Pain

The pathophysiological mechanisms underlying CPSP include central sensitization, alterations in spinothalamic tract function, disinhibition of sensory pathways, and specific thalamic changes.¹ Central sensitization involves anatomical, neurochemical, and inflammatory changes after CNS lesions, resulting in neuronal hyperexcitability. Alterations in the spinothalamic tract disrupt normal pain and temperature perception, potentially causing abnormal hyperactivity or persistent neuronal firing. Disinhibition theories

suggest reduced inhibitory control within sensory pathways due to damage to the lateral sensory systems, leading to enhanced pain signaling by medial pain systems.¹⁴ Moreover, thalamic changes are significant, where lesions in nuclei like the ventral posterior lateral (VPL) or ventral posterior medial (VPM) can disrupt sensory modulation, leading to dysesthesia and central pain. Functional imaging studies show reduced regional cerebral blood flow in thalamic areas during spontaneous pain episodes and increased neuronal activity indicative of hyperexcitability. Additionally, abnormal oscillatory patterns between the thalamus and cortical regions, known as reverberation, have been implicated in sustaining chronic central pain conditions.¹⁵

Understanding these complex mechanisms is crucial for improving CPSP diagnosis, prognosis, and management strategies, thereby enhancing post-stroke patient outcomes and quality of life.

Management and Psychosocial Considerations of Central Post-Stroke Pain (CPSP)

Management of Central Post-Stroke Pain (CPSP) remains challenging due to its variable responsiveness to treatment and the complexity of associated symptoms, especially among elderly populations where medication side effects often limit therapeutic dosing.¹⁶ Current clinical practices primarily involve trial-and-error pharmacological approaches, frequently employing combinations of medications, though few rigorous randomized controlled trials (RCTs) are available. Notably, a placebo-controlled trial investigating prophylactic amitriptyline (75 mg/day) following acute thalamic stroke demonstrated no significant preventive effects.¹⁶

Pharmacologically, antidepressants, particularly tricyclic antidepressants like amitriptyline, are considered first-line treatments for CPSP, effectively reducing pain severity. However, side effects such as sedation and dry mouth remain common. Serotonin-norepinephrine reuptake inhibitors (SNRIs) may offer a safer alternative, particularly for patients with cardiovascular risks, whereas selective serotonin reuptake inhibitors (SSRIs) generally appear less effective for neuropathic pain.¹⁶ Anticonvulsants, including gabapentin and pregabalin, effectively reduce neuropathic pain by decreasing neuronal hyperactivity. Pregabalin, specifically, has shown substantial clinical benefit and acceptable tolerability. Lamotrigine offers moderate effectiveness but has inconsistent efficacy in central neuropathic conditions, whereas carbamazepine demonstrated minimal benefit for CPSP.¹⁶ Opioids, although effective for neuropathic pain, are generally second-line therapies due to their side-effect profiles, withdrawal rates, and limited long-term effectiveness in CPSP populations.

Psychosocial factors, notably self-efficacy, psychological flexibility, and coping strategies, significantly impact CPSP management outcomes. Chronic post-stroke pain patients frequently demonstrate low self-efficacy, limited psychological flexibility, and maladaptive coping behaviors, negatively affecting

quality of life. Promising evidence suggests enhancing psychological flexibility and self-efficacy through motivational interviewing and structured psychological therapies can substantially improve chronic pain management outcomes in stroke survivors. However, further studies with larger sample sizes are necessary to comprehensively validate these psychosocial interventions and integrate them effectively into CPSP management protocols.¹⁷

Exercise Interventions in the Medical Rehabilitation of Central Post-Stroke Pain (CPSP)

Central Post-Stroke Pain (CPSP) presents significant rehabilitation challenges due to its persistent nature and impact on functional recovery. Exercise therapy, widely recognized as a cost-effective and accessible intervention, plays a crucial role in managing CPSP, enhancing functional capacity, and improving the overall quality of life of stroke survivors ¹⁸

Exercise interventions for CPSP primarily involve strength training, aerobic conditioning, flexibility exercises, and innovative approaches like mirror therapy. Regular structured exercise has been shown to reduce pain intensity, enhance neural plasticity, modulate inflammatory processes, and ultimately improve neurological and functional outcomes post-stroke.¹⁹

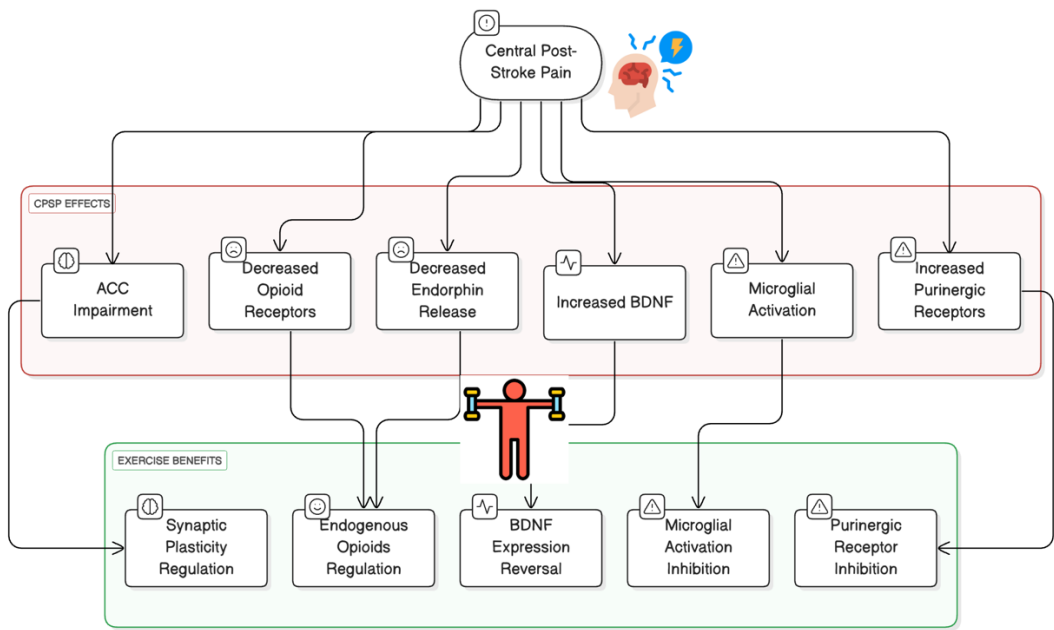


Figure 2. Exercise Mechanism to reduce Central pain post stroke

Strength training significantly alleviates CPSP by reducing muscle weakness, increasing pain thresholds, and minimizing pain sensitivity. Recommended protocols include resistance exercises targeting major muscle groups at intensities ranging from 30% to 80% of one repetition maximum (1-RM), performed two to three times per week.²⁰ A randomized clinical trial using structured band-resistance and range-of-motion

training demonstrated notable reductions in pain severity, highlighting the therapeutic value of progressive strength exercises.²¹

Aerobic training, an integral component of post-stroke rehabilitation, effectively manages CPSP through cardiovascular health enhancement and analgesic mechanisms, including modulation of central sensitization and inflammatory cytokines.²² Standard aerobic exercise guidelines recommend moderate-intensity sessions (40%–59% of heart rate reserve), performed 20–40 minutes per session, three to five times weekly, progressively increasing intensity and duration according to individual patient tolerance.²³

Flexibility exercises, particularly stretching and therapeutic yoga, address musculoskeletal complications frequently seen post-stroke, such as muscle spasms, joint contractures, and limited range of motion. Studies by Schmid et al. (2014) indicate that an eight-week structured yoga intervention significantly decreases CPSP severity and improves patient-reported quality of life.²⁴ Flexibility exercises should ideally be integrated into daily routines to maintain muscle length, joint mobility, and functional independence.²⁵

Mirror therapy, another innovative exercise intervention, utilizes visual feedback mechanisms to correct maladaptive somatosensory cortex reorganization associated with CPSP. This therapy improves sensory-motor congruence, reducing the perception of pain through cortical recalibration and restoration of sensory integration.²⁶

Neurobiologically, exercise interventions stimulate neural adaptations critical for pain modulation. Exercise-induced enhancements in brain-derived neurotrophic factor (BDNF), endogenous opioid systems, inhibition of microglial activation, and regulation of neuroinflammatory markers have been identified as potential analgesic mechanisms. These adaptations collectively foster neural plasticity, reduce central sensitization, and improve functional recovery.²²

Complementing exercise, neuromodulation techniques have emerged as promising adjunctive therapies for CPSP. High-frequency repetitive transcranial magnetic stimulation (rTMS), particularly when applied over the primary motor cortex (M1), is currently the most extensively studied non-invasive brain stimulation technique. Randomized controlled trials have demonstrated significant reductions in pain intensity immediately after treatment, with analgesic effects persisting for approximately two to four weeks. The proposed mechanism involves modulation of cortical excitability, restoration of thalamocortical connectivity, and activation of descending inhibitory pain pathways. Although the short-term efficacy of rTMS is well established, maintenance protocols and optimal stimulation parameters remain under investigation.²⁷ Transcranial direct current stimulation (tDCS) is another non-invasive neuromodulation technique that delivers low-intensity electrical currents to modulate cortical activity. Several clinical studies have demonstrated

reductions in pain intensity and improvements in sensory discrimination following stimulation of the primary motor cortex. Compared with rTMS, tDCS is less expensive, portable, and easier to implement in clinical settings, although its analgesic effects appear to be smaller and evidence remains limited.²⁸ Deep Brain Stimulation (DBS) represents an invasive neurosurgical option reserved for patients with refractory CPSP who fail conventional pharmacological and rehabilitation treatments. DBS commonly targets the periventricular/periaqueductal gray matter or sensory thalamic nuclei to modulate abnormal pain processing. Although several observational studies have reported clinically meaningful pain relief, current evidence is insufficient to recommend DBS as routine treatment because of limited randomized controlled trials and potential surgical risks.²⁹ Acupuncture and electroacupuncture, derived from traditional Chinese medicine, have also demonstrated comparable analgesic effectiveness to pharmacological approaches, providing valuable adjunctive treatment strategies.

Psychosocial interventions, including Cognitive Behavioral Therapy (CBT) and Acceptance and Commitment Therapy (ACT), are pivotal components of comprehensive CPSP rehabilitation. CBT helps patients reduce pain perception and improve psychological adjustment through structured skill-building techniques such as cognitive restructuring, relaxation, and activity pacing.³⁰ ACT further enhances coping mechanisms by promoting psychological flexibility, mindfulness, and cognitive defusion, facilitating better acceptance and management of chronic pain experiences, thus improving overall quality of life.³¹

Implementing an individualized, multidisciplinary rehabilitation strategy that integrates structured exercise, targeted physical modalities, and tailored psychosocial interventions is essential to optimize pain management, enhance functional independence, and significantly improve the long-term outcomes of CPSP patients. Continued rigorous research is warranted to refine these integrated rehabilitation approaches and establish standardized, evidence-based protocols for CPSP management.

Conclusion

Rehabilitation for Central Post-Stroke Pain (CPSP) requires a comprehensive, multidisciplinary approach due to its complex nature and significant impact on quality of life. Structured physical exercise remains a key component of CPSP management, as it improves pain, mobility, muscle strength, and functional recovery when tailored to individual patient needs. Current evidence suggests that progressive resistance and aerobic exercise performed for approximately 8–12 weeks provide the most consistent clinical benefits.

Psychosocial interventions, including Cognitive Behavioral Therapy (CBT) and Acceptance and Commitment Therapy (ACT), together with patient education, are essential for improving coping strategies, treatment adherence, and self-management. Ongoing monitoring and collaboration among healthcare providers, patients, and families are also crucial to optimize rehabilitation outcomes.

Among adjunctive rehabilitation modalities, repetitive transcranial magnetic stimulation (rTMS) has the strongest evidence for short-term pain relief, whereas transcranial direct current stimulation (tDCS) may be considered an alternative non-invasive option. Deep Brain Stimulation (DBS) should be reserved for carefully selected patients with refractory CPSP because of its invasive nature and limited clinical evidence. Future high-quality studies are needed to establish standardized rehabilitation protocols regarding treatment intensity, duration, and long-term effectiveness.

Conflict of Interest

The author declares that there is no conflict of interest related to the content of this manuscript.

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References

1. Klit, H., Finnerup, N. B. & Jensen, T. S. Central post-stroke pain: clinical characteristics, pathophysiology, and management. *The Lancet Neurology* vol. 8 857–868 Preprint at [https://doi.org/10.1016/S1474-4422\(09\)70176-0](https://doi.org/10.1016/S1474-4422(09)70176-0) (2009).
2. Yam, M. *et al.* General Pathways of Pain Sensation and the Major Neurotransmitters Involved in Pain Regulation. *Int J Mol Sci* 19, 2164 (2018).
3. Khalid, S. & Tubbs, R. S. Neuroanatomy and Neuropsychology of Pain. *Cureus* 9, e1754 (2017).
4. McEntire, D. M. *et al.* Pain transduction: a pharmacologic perspective. *Expert Rev Clin Pharmacol* 9, 1069–1080 (2016).
5. Vadivelu, N., Whitney, C. J. & Sinatra, R. S. Pain Pathways and Acute Pain Processing. in *Acute Pain Management* 3–20 (Cambridge University Press, 2009). doi:10.1017/CBO9780511576706.003.
6. Cambier, J. [Dejerine-Roussy syndrome]. *Rev Neurol (Paris)* 138, 979–88 (1982).
7. Head, H. & Holmes, G. Sensory Disturbances From Cerebral Lesion. *Brain* 34, 102–254 (1911).
8. Treede, R.-D. *et al.* Neuropathic pain: redefinition and a grading system for clinical and research purposes. *Neurology* 70, 1630–5 (2008).
9. Kim, J. S. Central post-stroke pain or paresthesia in lenticulo-capsular hemorrhages. *Neurology* 61, 679–682 (2003).
10. Widerström-Noga, E., Loeser, J. D., Jensen, T. S. & Finnerup, N. B. AAPT Diagnostic Criteria for Central Neuropathic Pain. *J Pain* 18, 1417–1426 (2017).
11. Westerlind, E., Singh, R., Persson, H. C. & Sunnerhagen, K. S. Experienced pain after stroke: a cross-sectional 5-year follow-up study. *BMC Neurol* 20, 4 (2020).
12. Kim, J. S. Post-stroke pain. *Expert Review of Neurotherapeutics* vol. 9 711–721 Preprint at <https://doi.org/10.1586/ern.09.19> (2009).
13. Bogousslavsky, J., Regli, F. & Uske, A. Thalamic infarcts. *Neurology* 38, 837–837 (1988).
14. (Bud) Craig, A. D. A new version of the thalamic disinhibition hypothesis of central pain. *Pain Forum* 7, 1–14 (1998).
15. Bashir, A. H., Abdullahi, A., Abba, M. A. & Mukhtar, N. B. Central Poststroke Pain: Its Profile among Stroke Survivors in Kano, Nigeria. *Behavioural neurology* 2017, 9318597 (2017).
16. Kumar, B., Kalita, J., Kumar, G. & Misra, U. K. Central poststroke pain: A review of pathophysiology and treatment. *Anesth Analg* 108, 1645–1657 (2009).
17. Mohan, A. T. *et al.* Stroke-Induced Central Pain: Overview of the Mechanisms, Management, and Emerging

- Targets of Central Post-Stroke Pain. *Pharmaceuticals* vol. 16 Preprint at <https://doi.org/10.3390/ph16081103> (2023).
18. Zhang, Y.-H. *et al.* Exercise for Neuropathic Pain: A Systematic Review and Expert Consensus. *Front Med (Lausanne)* 8, (2021).
 19. Kim, Y. *et al.* Exercise Training Guidelines for Multiple Sclerosis, Stroke, and Parkinson Disease. *Am J Phys Med Rehabil* 98, 613–621 (2019).
 20. Han, P. *et al.* Clinical Evidence of Exercise Benefits for Stroke. in 131–151 (2017). doi:10.1007/978-981-10-4304-8_9.
 21. Vahlberg, B., Lindmark, B., Zetterberg, L., Hellström, K. & Cederholm, T. Body composition and physical function after progressive resistance and balance training among older adults after stroke: an exploratory randomized controlled trial. *Disabil Rehabil* 39, 1207–1214 (2017).
 22. Ma, Y., Luo, J. & Wang, X.-Q. The effect and mechanism of exercise for post-stroke pain. *Front Mol Neurosci* 15, (2022).
 23. Öte Karaca, Ş., Demirsoy, N. & Günendi, Z. Effects of aerobic exercise on pain sensitivity, heart rate recovery, and health-related quality of life in patients with chronic musculoskeletal pain. *International Journal of Rehabilitation Research* 40, 164–170 (2017).
 24. Schmid, A. A., Miller, K. K., Van Puymbroeck, M. & DeBaun-Sprague, E. Yoga leads to multiple physical improvements after stroke, a pilot study. *Complement Ther Med* 22, 994–1000 (2014).
 25. Bastille, J. V & Gill-Body, K. M. A Yoga-Based Exercise Program for People With Chronic Poststroke Hemiparesis. *Phys Ther* 84, 33–48 (2004).
 26. Ramachandran, V. S. & Altschuler, E. L. The use of visual feedback, in particular mirror visual feedback, in restoring brain function. *Brain* 132, 1693–1710 (2009).
 27. Hosomi, K. *et al.* Daily repetitive transcranial magnetic stimulation of primary motor cortex for neuropathic pain: A randomized, multicenter, double-blind, crossover, sham-controlled trial. *Pain* 154, 1065–1072 (2013).
 28. Bae, S. H., Kim, G. Do & Kim, K. Y. Analgesic effect of transcranial direct current stimulation on central post-stroke pain. *Tohoku Journal of Experimental Medicine* 234, 189–195 (2014).
 29. Katayama, Y., Tsubokawa, T. & Yamamoto, T. Chronic Motor Cortex Stimulation for Central Deafferentation Pain: Experience with Bulbar Pain Secondary to Wallenberg Syndrome. *Stereotact Funct Neurosurg* 62, 295–299 (1994).
 30. Keefe, F. J., Porter, L., Somers, T., Shelby, R. & Wren, A. V. Psychosocial interventions for managing pain in older adults: outcomes and clinical implications. *Br J Anaesth* 111, 89–94 (2013).
 31. Harrison, R. A. & Field, T. S. Post stroke pain: Identification, assessment, and therapy. *Cerebrovascular Diseases* vol. 39 190–201 Preprint at <https://doi.org/10.1159/000375397> (2015).