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Main causes of phantom limb pain after amputation: an integrative review

Abstract

Introduction: Phantom Limb Pain (PLP) is characterized in most cases of amputa-tion, causing pain and emotional discomfort to the patient, which compromises quality of life. Objective: identify the main factors related to the cause of phantom limb pain.

Methodology: This is an integrative review carried out between September and Octo-ber 2022, on the Pubmed and Virtual Health Library (VHL) platforms. The following search strategy was applied: ("Phantom Limb" OR pseudomelia) AND pain AND ampu-tation AND (causality OR factors), according to the Health Sciences Descriptors system and articulated by Boolean operators.

Results: The present study found 12 articles, it was observed that the majority of FMD cases occur due to amputations due to cancer and that, among its possible contributing factors, amputations of limbs at a level more proximal to the axial skeleton stand out, especially in losses above the level of the knee and above the level of the wrist, preoperative pain, with a tendency to generate a so-matosensory memory and promote pain in the same location with similar intensity after amputation, applied anesthesia, simultaneous treatments of adverse diseases, psychological problems, such as depression and anxiety, and brain maladaptations associated with the peripheral nervous system and body representation, the latter in a way that favors changes that allow pain circuits to be functionally more active. The groups most likely to acquire PLP are women and individuals with less education. Patients mainly reported electrical sensations, itching, and a sensation of movement as manifestations of PLP. Despite the findings, there are certain contradictions between different studies available.

Conclusion: The main causes of phantom limb pain are preoperative pain, psychological factors, the level of amputation and neurophysiological reorganization, and it is necessary to understand these causes with a view to the well-being and comfort of patients.

Keywords: main factors, amputation, pain, phantom limb

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Introduction

Phantom Limb Pain (PLP) has a frequency of 50% to 80% in cases of surgical or traumatic amputation, so that it predominates in the upper limbs.[1] According to the World Health Organization (2022), in the International Code of Diseases (ICD-11), the phantom limb is characterized by different sensations in the amputated limb, such as temperature, pain, tingling, itching, paresthesia or sensation of movement. In this sense, PLP can manifest itself in association with the sensation of the phantom limb and pain in the residual limb.[2] As a result, the disease's ability to compromise the quality of life and autonomy of amputees is considerably high.[3]

Pain, which causes significant discomfort in these patients, is defined by the Board of Directors of the Brazilian Society for the Study of Pain.[4,] P1 as "an unpleasant sensory and emotional experience associated, or similar to that associated, with some actual or potential tissue damage". According to Carvalho and Parsons,[5] Pain can be classified depending on its pathophysiology, being nociceptive, neuropathic or mixed. In the first, nociceptive neurons are activated in the skin tissue (somatic pain) or internal tissue (visceral pain). In neuropathy, nociceptors are altered due to damage to the spinothalamic tract (central pain) or damage to the peripheral nervous system (peripheral pain). In some cases, although the pain appears to be related to the central nervous system, the injury is related to the peripheral system, which is the case with PLP.

It is important to highlight that PLP is more prevalent in cases of amputation due to cancer, and in this case, pain is associated with demographic factors, such as age, sex, tobacco use, marital status and level of amputation, pre- operative factors, factors related to treatment, such as chemotherapy and radiotherapy, intraoperative and postoperative factors.[6]

Considering the great prevalence of the disease and its characteristic of directly affect-ing the well-being of patients, the need to identify the main factors that cause pain in the phantom limb becomes evident.

Methodology

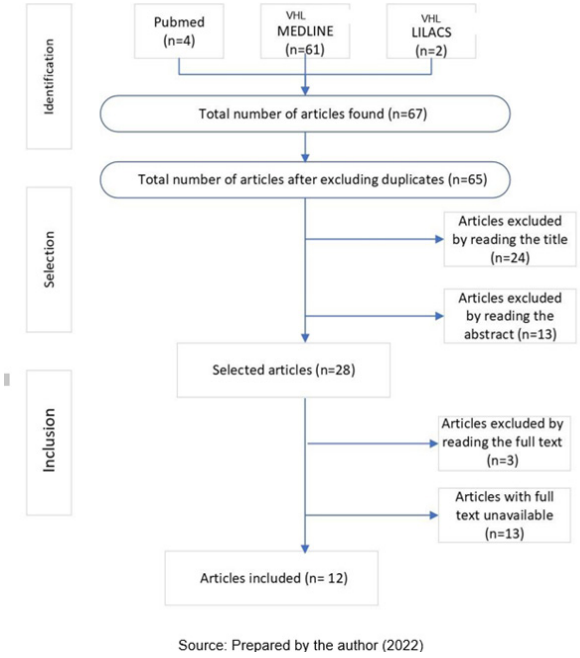
This integrative review aims to bring together scientific knowledge, according to a defined research methodology covering different types of studies, on the topic introduced above. To this end, the following question guiding the work was established: "What are the main factors that cause a sensation of pain at the site of the phantom limb?" Given this delimitation, the research design and data collection took place between September and October 2022, on the Pubmed and Virtual Health Library (VHL) platforms. In these, the search strategy was applied by combining the descriptors ("Phantom Limb" OR pseudomelia) AND pain AND amputation AND (causalityThis integrative review aims to bring together scientific knowledge, according to a defined research methodology covering different types of studies, on the topic introduced above. To this end, the following question guiding the work was established: "What are the main factors that cause a sensation of pain at the site of the phantom limb?" Health Sciences and articulated by Boolean operators.

Thus, the inclusion criteria for the research were articles with publication dates be-tween 2017 and 2022, in Portuguese and English and with full and free text availability, so that literature reviews, clinical practice guides and meta-analyses were excluded. In Pubmed, filters for clinical trial and randomized controlled trial studies were selected. In the VHL, filters were selected with studies such as risk factors, case reports, controlled clinical trials, etiology studies, prognostic studies, prevalence studies, incidence studies, observational studies, diagnostic studies, assessment of health technologies and tracking study.

After the search strategy, a staged selection strategy was used by reading the title, abstract and full text, with the aim of ensuring that the articles were compatible with the proposed theme and research objective.

Results

67 articles were found, four of which were available in PubMed (MEDLINE) and 63 in the VHL (61 from MEDLINE and two from LILACS). Of these, two articles were excluded due to duplicates, 24 due to reading the title, which was not consistent with the delimited theme in question, and 13 due to reading the summary, which clarified the use of methodologies that diverged from those established by the search strategy, and in-depth studies not compatible with the proposed question. Thus, with 28 remaining articles, three were excluded due to the complete reading of the text, given the deviation from the focus on the objective of this work, and another 13 were discarded due to their complete text, which was however unavailable. As a result, 12 articles were selected to integrate the present study (Figure 1) (Table 1 & 2).



Source: Prepared by the author (2022)

Figure 1 Article selection flow diagram.

Table 1 Studies included in the integrative review classified according to title, authorship, year of publication, country of study and type of study

Title	Authorship	Year	Country	Type of study
Prevalence of Phantom Limb Pain, Stump Pain, and Phantom Limb Sensation among the Amputated Cancer Patients in India: A Prospective, Observational Study	Ahmed et al.	2017	India	Prospective and Observational
Association between phantom limb complex and the level of amputation in lower limb amputee	Kelle et al.	2017	Turkey	Retrospective review
Long-term symptoms and function after war-related lower limb amputation: A national cross-sectional study	Esfandiari et al.	2018	Iran	cross-sectional study
Resting TcPO2 levels decrease during liner wear in persons with a transtibial amputation	Berli et al.	2020	Switzerland	cross-sectional study
Benchmarking Residualm Limb Pain and Phantom Limb Pain in Amputees through a Patient-reported Outcome Survey	Mioton et al.	2020	USA	cross-sectional study
Protective and Risk Factors for Phantom Limb Pain and Residual Limb Pain Severity	M¨unger et al.	2020	USA	Cross-sectional analysis of a randomized controlled trial
Structural and functional motor cortex asymmetry in unilateral lower limb amputation with phantom limb pain	Pacheco Barrios et al.	2020	USA	Cross-sectional analysis of a randomized controlled trial
Phantom eye pain: a multicentric study in 100 patients	Martel et al.	2021	France	Multicenter study
Phantom Limb Pain and Sensations in Chinese Malignant Tumor Amputees: A Retrospective Epidemiological Study	Jiang et al.	2021	China	Retrospective study
Early application of cryoanalgesia to the brachial plexus prevents development of phantom limb pain after traumatic forequarter amputation: A case report	O'Connor et al.	2022	USA	Case report
Sex-specific Differences in Multi site Pain Presentation among Adults with Lower-Limb Loss	Beisheim et al.	2022	USA	Cross- sectional study
The Recurrence of Phantom Limb Pain with Spinal Anesthesia	Lee et al.	2022	South Korea	Case report

Source: Prepared by the author (2022).

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Table 2 Main results found in the articles above

1	Demographics were subdivided into age, sex, married status, and whether the individual smoked. Regarding age, individuals under 30 years old and between 51 and 60 had a higher incidence of PLP, between 51 and 60 a higher incidence of pain in the stump and sensation of PL. As for other factors, all data indicate the prevalence of PLP, stump pain and MF sensation in females, married individuals and smokers. In addition to demographic factors, PL was also caused by pre-operative factors, related to the treatment of other diseases - such as chemotherapy and radiotherapy, both with a prevalence of PLP development intra and post-operatively.
2	Phantom limb pain is possibly related to brain mal-adaptations or peripheral and spinal factors, and may involve a lack of perception of body representation in the somatosensory and motor cortex in the face of the injury. Given a sample of patients who suffered amputations at different levels of the lower limb and who had no follow-up for the PLP condition, groups were created to evaluate the prevalence of PLP, in terms of frequency and intensity of pain, in the initial post-mortem period surgery and six months after surgery. A prevalence of PLP was found in patients who underwent amputations above the knee level or below the ankle level, only in the initial postoperative period. Six months after surgery, there was neither much prevalence nor divergence in the occurrence of this condition between the groups. Furthermore, no relationship was found between preoperative pain and PLP. Despite these results, studies on this aspect as a potentiator or not of the disease are conflicting and, therefore, not well explained.
3	Transfemoral amputation, knee disarticulation and hip disarticulation in war soldiers proved to be very relevant in terms of FMD, since 62% of amputees had this sequel even years after the incident, with the occurrence varying with the height of the incident amputation.
4	When trying to relate the resting oxygen level in the tissues with the prevalence of PL, it was found that sex was the only factor with a probable relationship between the other tests performed.
5	Of the people whose responses were analyzed, the majority reported the cause of amputation as being related to trauma, followed by infection, ischemia and diabetes. Most interviewees suffered lower limb amputation, mainly below the knee. Further-more, the majority of interviewees had phantom limb pain (PLP), to the detriment of residual limb pain (RLP). A score of 46.8 (on a scale of 41 to 54) was obtained for PLP in the Patient Reported Outcomes Measurement Information System, based on the average of pain intensity and pain behavior scores. In individuals with RLP, a score of 46.6 was obtained. The median pain score was 4 (on a scale of 0-10) and, among amputees, only 26.9% reported the absence of FMD and 25.4% the absence of FLP. The groups most likely to present PLP and RLP were women and those with the lowest level of education. Cancer patients were less likely to acquire PLP when compared to victims of amputations due to non-military causes, and amputees who suffered from infection and ischemia had a higher incidence of PLP. Further-more, the chance of obtaining PLP in the first year of amputation was greater, when compared to the chance after 10 years or more. Finally, more proximal upper and lower limb amputees were more likely to suffer from PLP than those who underwent below-knee amputations.
6	Patients who participated in the research reported electrical sensations, itching and sensations of movement as the main symptoms of phantom limb pain. Lower pain intensity was observed in individuals who consume opioids and in patients who experience more frequent pain. Correlations with age and time since amputation showed no statistically significant differences. In multivariate analysis, it was found that age and intensity of phantom limb sensations were positive predictors of phantom limb pain intensity, while presence of movement sensation and response to previous treatment were negative predictors.
7	The study included 62 traumatic unilateral lower limb amputees with an average PLP of 5.9. We found, in the affected hemisphere, an anterior displacement of the center of gravity of the hand area (23mm, CI 95%) and a disorganized and generalized representation. Regarding the analysis of gray matter asymmetry, data from 21 participants show a loss of gray matter volume in the motor area of the affected hemisphere. This asymmetry appears negatively associated with time since amputation. For transcranial magnetic stimulation data, only the intracortical facilitation ratio is negatively related to PLP intensity
8	No estudo internacional multicˆentrico foram observados fatores que podem aumentar o risco da ocorrˆencia de dor no olho fantasma (PEP), dentre eles s˜ao a dor ocular pr´e-operat´oria (p = 0,031), o glaucoma (p = 0,027), a ansiedade p´os-operat´oria com HADS ≥ 8 (p = 0.012) e ≥ 11 (p = 0.014) e o desconforto est´etico (p = 0,002).
9	The article found no differences in data on age, sex, time of amputation, dominant side, types of anesthesia and perioperative chemotherapy, conflicting results were found regarding preoperative pain and incidence of PLP, and found no difference in the incidence of PLP between amputation of upper and lower limbs; but found a difference in the incidence of PLP at amputation levels (below or above the wrist), suggesting that the level of amputation is more responsible for PLP
10	The case report demonstrates the efficiency of intraoperative cryoanalgesia for the prevention of FMD, as the procedure blocks the peripheral nerve responsible for carrying the painful stimulus to the central nervous system and for preserving structural elements of the nerve bundle (endoneurium, epineurium and perineurium), allows nerve regeneration.
11	The prevalence of pain in the phantom limb was similar between the sexes, in relation to pain in the residual limb it was more common in females (53.0%) than in males (38.4%) Sixty percent of the sample reported multisite pain, being more prevalent in females (72.0%) compared to males (54.7%).
12	The article indicates that regional lockdowns can induce PLP, states that psycho-logical factors such as depression, anxiety and post-traumatic stress are risk factors for PLP.

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Discussion

Possible neurological causes of PLP

Pre-operative pain: In the study by Jiang et al.,[7] the presence of preoperative pain was a significant factor in the incidence of PLP, of the 88 interviewees, 52 (59%) had preoperative pain, generally caused by septic skin ulcers, tissue distension, swelling or infection. According to Ahmed et al.[6] the preoperative factors that showed the highest prevalence of PLP were pain, illnesses and concerns related to amputation, because they were associated with almost 50% of those affected. Accordingly, Larbig et al.[8] concluded that preoperative intervention is important to prevent chronic PLP as it interrupts the neural memory of pain. However, Kooijman et al.[9] state that preoperative pain is not related to FMD in upper limb amputation.

Preoperative pain could be one of the main associated factors due to the stimulus generated in the somatosensory cortex, which promotes somatosensory memory, which can be activated even after amputation. In the study by Katz and Melzack,[10] it was observed that the intensity and location of preoperative pain continued even after limb amputation.

Amputation level and difference between upper and lower limb: According to the findings of Kelle et al.,[11] the prevalence of FMD was more significant in patients who underwent amputations above the knee level or below the ankle level. Regarding amputations in the upper limb, a higher occurrence of FMD was found in patients who suffered losses above the level of the wrist.[7]. According to Gabarra and Crepaldi,[12] it is possible that this is justified, especially in the case of amputa-tion in proximal regions, due to the difficulty of rehabilitation and resumption of daily activities in the initial postoperative period, a fact that can even present psychological correlations with feelings of frustration and poor adaptation to the patient's new reality, given the greater body loss. Despite this, the interference of the level of amputation in the occurrence of FMD presents divergences in different studies, whether due to the quantitative limitation of the sample or non-standard amputation conditions, such as the variety of etiology of this loss or analyzes focused in isolation on lower or upper limbs, without cross comparison.[11]

In addition to the aforementioned aspect, according to an analysis carried out by Kelle et al.,[11] a decrease in the prevalence of attacks and the incidence of PLP was found over the time since amputation, which is an indicative factor of gradual neurophysiological reorganization. In line with this finding, data from the study by Teixeira et al.[13] and the study by Mioton et al.[14] also confirm a greater predominance of phantom limb pain in patients with shorter amputation time among monitored participants. Thus, we note some relevant findings for the identification of contributing factors to FMD, but it is worth highlighting the need for in-depth studies and larger-scale studies, to enable a broader view of the problem discussed.

Psychological factors: According to a study carried out by Gabarra and Crepaldi,[12] amputation surgery causes emotional fragility in the patient, as this situation generates uncertainty and fears about the consequences generated by this process. Anxiety affects the individual from the moment the surgery decision is made to the preoperative and postoperative periods, due to the feeling of incapacitation, loss of independence and separation from work and family. Therefore, it is very important that doctor-patient communication about attempts to save the limb and the impossibility of doing so is done in a frank and honest manner, so that the benefits of the surgery and the short and long-term implications are presented clearly to the patient. The facts presented are in line with the study by Mioton et al.,[14] which states that amputation results in lifelong emotional effects.

Anxiety and stress that precede amputation can also be predictive factors for Phan-tom Limb Pain (MFD), affecting three quarters of amputees.[14] Furthermore, patients who do not receive sufficient emotional support before amputation report more episodes of FMD. In this way, individuals in need of emotional help suffer more intensely from the consequences of FMD, as the patient can experience it very frequently and with great intensity, which generates daily stress, reducing their psychological well-being and increasing their need for medication and health services.[12]

In view of the factors presented, the importance of a psychologist's role in helping the patient to deal with the suffering resulting from the consequences of surgery is clear, which includes the feeling of mourning for the loss of a limb and depressive feelings, in addition to seeking to minimize episodes of DMF, as the therapy would help the patient to control preoperative anxiety, which seems to be a determining factor for the occurrence of DMF. Furthermore, social and family support is essential to guarantee the well-being of amputees, mainly because it is a time of adaptation and reevaluation of life.[12]

Neurophysiological reorganization: Pain, pressure, temperature and protopathic touch are transported sensitively to the postcentral gyrus of the parietal lobe, called the primary somatosensory cortex, through the anterolateral system of the spinal cord. In the case of pain and temperature, transport is precisely in the lateral spinothalamic tract to the parietal lobe. In detail, pain stimulated in one extremity is transported by a first-order pseudounipolar neuron in the posterior root ganglion and ascends to the thalamus via the second-order neuron, from the thalamus it goes to the somatosensory cortex via the third-order neuron.[15]

In the study by Pacheco-Barrios et al.,[2] a loss of gray matter volume was found in 21 of the patients who had pain in the phantom limb. This result is commonly reported in other studies because, after an amputation, there is an acute lack or rupture of afferents that were originally presented from the missing limb.

This rupture causes neurophysiological and structural reorganization changes in the motor cortex, which, according to Pacheco-Barrios et al.,[2] was characterized by a disorganized, disseminated and displaced cortical representation of the hand. Although this cortical reorganization does not correlate with the intensity of pain in lower limb amputees, it is possible to infer that it is related to the presence of PLP.

Complementarily, the study by Flor et al.[16] reinforces this conception in that it described an intense relationship between the amount of cortical reorganization and the magnitude of FMD after arm amputation. This data indicates that FMD is related to, and may be a consequence of, plastic changes in the somatosensory cortex. Thus, reorganization can provide the necessary changes for pain circuits to be func-tionally more active, while pain intensity is related to emotional-affective processing.

Despite the relevance of neurophysiological reorganization, it is still necessary to study other mechanisms such as cellular atrophy and synaptic reorganization to better under-stand the relationship between and gray matter volume.[2]

In another approach, O'connor,[1] suggests that PLP may be caused by the development of a neuroma in the peripheral nerves over time that contributes to painful sensations by continuing to provide negative information to the system central nervous system. The article by Flor[17] states that peripheral changes have been an im-portant factor in the development of PLP. When peripheral nerve damage occurs, its axons are regenerated by sprouting neuromas (disordered

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extensions of axons composed of type C fibers that are sensitive to stimuli), which generate more ectopic discharges, spontaneously or by pressure, which promote perception of pain.

Furthermore, according to Lee et al.,[18] the experience of PLP is due to abnormal input into the neuromatrix generated by amputation, which leads to an altered neurosignature.

Phantom eye pain

Phantom eye syndrome is described by the composition of any form of sensation observed by the patient around the ocular amputation, and it can be diagnosed if the patient presents one of the three symptoms that are pain in the phantom eye, phantom visions, characterized by seeing two images of a single object, and ghostly sensations..[19]

According to the questionnaires and studies prepared by Martel et al.,[19] of all patients who underwent eye amputation, around 47% of patients had phantom eye pain, 38% had phantom visions and 30

Among the most common factors for the occurrence of phantom eye pain is preoper-ative eye pain, which has already been highlighted in the[19] study. Furthermore, the memory of pain can be considered as a cause for this eye pain.

According to the study by Martel et al.,[19] glaocoma was related to pain in the phantom eye only in the univariate analysis ($p = 0.027$), without multivariate analysis, therefore it is not possible to analyze the total interference with pain. One fact that could be analyzed was the relationship between the way anesthesia is applied during surgery and eye pain in the phantom limb. Therefore, retrobulbar anesthesia is used as an efficient way to reduce pain in the postoperative period[20] since postoperative pain is related to the worsening and emergence of pain in the phantom eye.? this association would be possible, but no study has yet been able to confirm this relationship.

According to a questionnaire applied by Martel et al.,[19] around 34% and 42% of the patients interviewed had signs of anxiety and depression, respectively, with higher rates than previous studies, which makes An association of psychological illnesses with phantom eye pain is possible, but there is still no proof.

Prevalences of PLP

According to Ahmed et al.[6] PLP occurs with greater prevalence in cases of amputation due to cancer. The anesthesia applied can influence the occurrence of PLP, being the general one with the highest number of cases, not being influenced by the technique used. Pain normally begins on the postoperative day with intense pain, tingling symptoms, throbbing, among other characteristics, with the simultaneous appearance of two or more symptoms in most individuals. Furthermore, problems with the stump, such as friction with tissue and problems with the prosthesis, can influence the prevalence of PLP. The manifestation of the phantom limb (PL) occurs approximately one hour after surgery, however the duration varies in some studies. Some treatments for adverse diseases, such as cancer, also increased the prevalence of PLP, such as chemotherapy (increase in the late study period) and radiotherapy (increase in the early study period).

Furthermore, postoperative factors, such as local analgesia and neuroma, maintained a high prevalence. The intensity of pain remains unchanged throughout the study regard-less of gender, however, with different pain experiences due to hormonal and structural variation in the body. In agreement with the indifference of sex in PLP, studies by Berli et al.[21] also demonstrated that FMD does not differ according to sex and so-matic pathologies. However, in their study, there was a difference in tissue oxygen levels between the sexes, which did not affect the prevalence of PLP or PL.

With regard to the quality of life of these individuals, there is an important reduction related to the mental and physical discomfort caused by PL. According to Esfandiari et al., amputation at more proximal levels, in addition to increasing cases of PLP, causes mobility difficulties, pain in the collateral leg, low back pain and hip unevenness. In line, Ahmed et al.[6] observed that the prevalence of PLP decreases the performance status, which is an attempt to calculate the quality of life, of amputees.

Therefore, it is clear that there is much to be explored within the scope of PLP and technological advances that can contribute to new learning and ways of providing comfort and well-being to amputee patients. To this end, a better understanding of the factors related to its occurrence is important, making the development of further research for this purpose relevant, a fact that justifies the importance of this work.

Conclusion

Considering that PLP is a condition with high prevalence in amputee patients, this integrative review contributes to indicating risk factors for this condition that affects the quality of life of this specific population. In light of this idea, pre- and post-operative circumstances were recognized as potential causes, which could be related to exacerbated and uncontrolled pain, for example, and the level of amputation of the limb, so that more proximal ones proved to be more predictive of DMF. This causal relationship can also include psychological states of vulnerability, such as depression and anxiety, and treatments for adverse diseases simultaneously with the patient's amputation, such as chemotherapy.

In addition to these indicators, there are studies and hypotheses that identify PLP as a brain reorganization and readaptation response to body loss, with displacement or loss of the gray matter center and even readjustments of body representation. From this perspective, attempts to treat PLP themselves consist of tools for discoveries about the pathophysiology of this condition, since interventions based on peripheral nerve regen-eration and blockade of nerve endings have shown promising results, opening potential perspectives for future treatments.

Acknowledgments

None.

Conflicts of interest

The authors declare that there are no conflicts of interest.

References

1. O'Connor LA, Houseman B, Taffe D, et al. Early application of cryoanalgesia to the brachial plexus prevents development of phantom limb pain after traumatic forequarter amputation: A case report. *Trauma Case Reports*. 2020;131(10):2375–2382.
2. Pacheco-Barrios K, Pinto CB, Velez FGS, et al. Structural and functional motor cortex asymmetry in unilateral lower limb amputation with phantom limb pain. *Clin Neurophysiol.* 2020;131(10):2375–2382.
3. Esfandiari E, Karimi A, Masoumi M, et al. Long-term symptoms and function after war-related lower limb amputation: a national cross-sectional study. *Acta Orthop Traumatol Turc.* 2018;52(5):348-351.

4. DeSantana JM, Perissinotti DMN, Oliveira Junior JO, et al. Definition of pain revised after four decades. 2020.
5. Carvalho RT, Parsons HA. Manual de cuidados paliativos ANCP. ANCP Academia Nacional de Cuidados Paliativos, 2012.
6. Ahmed S, Ahmed A, Bhatnagar S, et al. Prevalence of phantom limb pain, stump pain and phantom limb pain sensation among amputee cancer patients in India: A prospective, observational study. *Indian J Palliat Care*. 2017;23(1):24–35.
7. Jiang S, Zheng K, Wang W, et al. Phantom limb pain and sansations in chinese malignant tumor am-putees: a retrospective epidemiological study. *Neuropsychiatr Dis Treat*. 2021;17:1579–1587.
8. Larbig w, Andoh J, Huse E, et al. Pre- and postoperative predictors of phantom limb pain. *Neurosci Lett.* 2019;702:44–50.
9. Kooijman CM, Dijkstra U, Geertzen J, et al. Phantom pain and phantom sensations in upper limb amputees: an epidemiological study. *Pain.* 2000;87(1):33–41.
10. Katz J and Melzack R. Pain "memories" in phantom limbs: review and clinical observations. *Pain.* 1990;43(3):319–336.
11. Kelle B, Kozano˘glu E, Bi¸cer OS, et al. Association between phantom limb complex and the level of amputation in lower limb amputee. *Acta Orthopaedica et Traumatologica Turcica*. 2017;51(2):142–145.
12. Gabarra LM, Crepaldi MA. The psychological aspects of amputation surgery. *Aletheia*. 2009;(30):59–72.
13. Teixeira G, Cardoso KA. Prevalence of pain and phantom sensation in lower limb amputees treated at the uni-centro physiotherapy school clinic teaching, research and extension integration week, 2009.
14. Mioton LM, Dumanian GA, Fracol ME, et al. Benchmarking residual limb pain and phantom limb pain in amputees through a patient-reported outcomes survey. *Plast Reconst Surg Global Open.* 2020;8(7):e2977.
15. Kaur A, Guan Y. Phantom limb pain: A literature review. *Chin J Traumatol.* 2018;21(06):366–368.
16. Flor H, Elbert T, Knecht S, et al. Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. *Nature.* 1995;375(6531):482–484.
17. Flor H. Phantom-limb pain: characteristics, causes, and treatment. *The Lancet Neurology*. 2022;1(3):182–189.
18. Lee SK, Park JE, Jin SY, et al. The recurrence of phantom limb pain with spinal anesthesia. *Niger J Clin Prac*. 2022;25(5):728–730.
19. Arnaud Martel, Stephanie Baillif, Pierre Thomas, et al. Phantom eye pain: a multicentric study in 100 patients. *Acta Ophthalmol.* 2021;99(5):e753–e760.
20. Calenda E, Benzerroug M, Retout A, et al. Duration of pain after a combination of peribulbar anesthesia and local anesthetic in the ball after enucleation or evisceration: 115 cases. *J Clin Anesth*. 2010;22(6):485–486.
21. Berli MC, Jundt-Ecker M, Meier MR, et al. Resting tcpo2 levels decrease during liner wear in persons with a transtibial amputation. *Plos one.* 2020;15(9):e0239930.

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