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The journal welcomes article submissions and does not charge any article submission fees.

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Aim:

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In essence, the journal aims to be a leading platform for researchers in various medical fields to share their findings with a global audience, contributing to the progress of medical knowledge.

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Research Article

The Relationship Between Kinesiophobia, Physical Activity and Disability Level and Pain Management in Patients with Chronic Low Back Pain in Genders

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ABSTRACT

The aim of this study was to examine the relationship between pain management, kinesiophobia, physical activity and disability level in patients with chronic low back pain (CLBP) in different genders. Eighty-two patients with CLBP (42 females, 42 males) between the ages of 20-60 participated in the study. Pain management strategies were determined by Pain Coping Questionnaire (PCQ). Tampa Scale for Kinesiophobia for perception of kinesiophobia, Oswestry Disability Index for disability due to pain and International Physical Activity Questionnaire-Short Form (IPAQ-SF) for the physical activity level were used. Women (mean age: 43.23±8.40 years) and men (mean age: 37.09±12.16 years) exhibited differences in helplessness ($p=0.001$) and conscious cognitive interventions ($p=0.023$) for pain management. No disparities were noted in self-coping and seeking medical help ($p>0.05$). Gender variation was significant in kinesiophobia ($p=0.002$), disability score ($p=0.031$), and disability percentage ($p=0.018$) among those with chronic low back pain. Notably, physical activity demonstrated gender balance ($p>0.05$), while sitting score had a significant difference ($p=0.000$). In both genders with CLBP, significant associations were found between PCQ dimensions and disability aspects, and in males, with physical activity ($p<0.05$). Management of CLBP varies by gender and is related to kinesiophobia, physical activity, and disability level.

Key words: chronic low back pain, pain coping, kinesiophobia, physical activity, disability

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INTRODUCTION

Chronic low back pain (CLBP) is an important problem widespread in society, whose prevalence has increased worldwide in recent years, leading to many disabilities. It accounts for many healthcare expenditures in countries (Shmagel ve ark., 2016). It is reported that CLBP is observed 2-3 times more frequently in women than in men (Skuladottir ve Halldorsdottir, 2008). Age, occupation, social status, and psychological factors are the most important factors in the development of CLBP. In addition, negative perceptions, attitudes, and the fear of re-injury with movement (kinesiophobia) are the most important factors influencing pain and pain-related disability (Picavet ve ark., 2002).

People with CLBP tend to avoid painful movements. Chronic pain causes fear, anxiety, and avoidance of movement, leading to decreased physical activity and increased disability (Ishak ve ark., 2017). As physical activity decreases, kinesiophobia also increases, which increases disability. Pain intensity is related to kinesiophobia and the fear of exercise to the degree of disability (Costa ve ark., 2011). When fear avoidance and kinesiophobia are present, secondary problems such as anxiety, depression, decreased quality of life, and recurrent chronic body pain occur. Studies suggest that people with

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kinesiophobia should gradually increase their functional activities (Costa ve ark., 2011; Filipczyk ve ark., 2021).

Chronic pain affects people physically, physiologically, mechanically, socially, economically, and psychologically. In chronic pain, people fear exercise and physical activity and develop various solutions to their pain (Karadağ ve ark., 2016; Peres ve Lucchetti, 2010). Some people accept chronic pain and develop new body adaptations (Peres ve Lucchetti, 2010). People with chronic pain need different strategies to cope with their pain. Pain management involves the human body's cognitive, emotional, behavioral, and physiological dimensions (Madenci ve ark., 2006). According to Snyder, coping with pain is a response to reduce stressful life events' physical, emotional, and psychological effects (Snyder, 1999). According to the manual, coping is the thoughts and actions of individuals in their daily efforts to deal with pain (Zeidner ve Endler, 1995). In a study of pain management or pain coping strategies, it was found that people with chronic pain tend to use methods of self-medication and deliberate cognitive interventions, and it was found that people with chronic pain of psychological origin fall into a state of helplessness (Peres ve Lucchetti, 2010).

Our study investigated the association between pain management, kinesiophobia, physical activity and disability level in individuals with CLBP in different genders.

MATERIAL AND METHODS

Individuals with CLBP aged 20–60 who met the inclusion criteria and volunteered to participate in the Fizyopilates Manual Therapy and Pilates Hall in the Alanya district of Antalya province participated in the study. All participants were given detailed information and written consent was obtained.

ETHICS COMMITTEE APPROVAL

The study was approved by Pamukkale University Non-Interventional Clinical Research Medical Ethics Committee with the decision dated 24.12.2019 and numbered 22. The study was conducted between December 2019 and December 2021. The power analysis used to determine the sample size showed that, at a 95% confidence level, a power of 80% would be achieved if at least 84 subjects (42 women and 42 men) were enrolled in the study (Faul ve ark., 2007).

One hundred twenty-six subjects were invited to study. The study was completed the 84 subjects, 42 women and 42 men. The flow chart of the study is shown in Fig 1.

INCLUSION CRITERIA

- Being between 20-60 years old,
- Having LBP lasting more than 3 months
- Those who had no problems with reading, writing and understanding.

EXCLUSION CRITERIA

- Had surgery due to back pain
- Had spine problem,
- Pregnancy,
- Those with communication problems

ASSESSMENT METHODS

All assessments were conducted personally by the researcher. Participants' demographic and clinical data were entered into the data collection form. Visual Analogue Scale (VAS) was used to pain intensity. The Pain Coping Questionnaire (PCQ) was used to inquire about the nature of pain coping, the Oswestry Disability Index (ODI) was used to assess disability level. Tampa scale of kinesiophobia (TSK) to assess perceptions of kinesiophobia, and the International Physical Activity Questionnaire-Short Form (IPAQ -SF) to assess levels of physical activity.

Demographic and clinical data form: Age, weight, height, sex, occupation, pain status, pain duration, pain definition, pain experience, pain frequency, conditions associated with pain, and conditions that exacerbate pain were recorded on the data collection form.

VAS: VAS was used to assess pain severity. Subjects were marked severity of pain on a 10-cm line. At lower values the pain is less and at higher values the pain gretater. The score was determined by the value of the marked point in cm (Chiarotto ve ark., 2019).

The PCQ was used to assess pain management. Kleinke developed this in 1992 for individuals with pain and the measures they took against pain and the methods they applied. The scale was developed for individuals with chronic pain and psychosomatic pain. Karaca et al. conducted the scale's validity and reliability study in 1996 and adapted it to the Turkish language. The scale has four subscales (self-coping, helplessness, conscious cognitive interventions, and seeking medical help) and consists of 29 items. The scale is a 4-point Likert type (0: never, 3:

Table 1. Demographic and clinical characteristics of the participants

Variable	Women (n=42) X±SD	Men (n=42) X±SD	t	p
Age (year)	43.23±8.40	37.09±12.16	2.69	0.009
BMI (kg/m2)	25.67±4.20	26.69±4.29	- 1.89	0.278
Pain duration (month)	63.04±92.90	46.40±64.03	0.95	0.342
VAS (cm)	6.15±1.66	5.25±2.28	1.99	0.049

Independent Samples t Test, BMI: Body Mass Index, VAS: Visual Analog Scale, X: Mean, SD: Standard deviation, p: Statistical Significance, t: Significance level of the test

often). The total score for each subscale is calculated by summing the scores for each item. The highest score that can be obtained on the scale is 36 points in the self-care subdimension, 24 in the helplessness and conscious cognitive intervention subdimension, 27 in the seeking medical help subdimension, and the lowest score that can be obtained on all subdimensions is 0 (Karaca ve ark., 1996). A high score ındıcates that the person's tendency to that technique has

The ODI was used to assess disability status. The ODI, whose validity and reliability were demonstrated in Turkey in 2004, it has 10 items such as severity of pain, personal care, lifting, walking, sitting, standing, social life, sleeping, traveling, and degree of pain. The higher the total score, the higher the degree of disability. The maximum score is 50 points. 31-50 points is evaluated as severe, 11-30 points as moderate and 1-10 points as mild. The degree of disability is determined based on the scoring (Durmuş ve ark., 2010; Yakut ve ark., 2004).

The TSK was used to assess kinesiophobia. This 17-item scale was developed by Miller et al. in 1991 and republished by Vlaeyen et al. in 1995. The Turkish validity and reliability was conducted by Yilmaz et al. in 2011. In the scoring system ranging from 17 to 68, kinesiophobia increases as the score increases (Yılmaz ve ark., 2011).

IPAQ - SF was used to assess physical activity. It is a test that includes questions for walking, sitting, high and moderate activities. The total score calculation includes the sum of time (minutes) and frequency (days) of walking, moderate activity, and vigorous activity. Turkish validity and reliability study of the scale was conducted by Ozturk (Craig ve ark., 2003; Öztürk, 2005).

Table 2. Pain management

Variable	Women (n=42) X±SD	Men (n=42) X±SD	t	p
Self management	19.07±7.86	16.54±7.57	1.49	0.138
Helplessness	12.52±4.66	9.11±4.73	3.32	0.001
Conscious cognitive intervention	12.76±5.29	10.11±5.14	2.32	0.023
Seeking medical help	12.50±4.93	10.80±5.26	1.51	0.133

Independent Samples t Test, X: Mean, SD: Standard deviation, p: Statistical Significance, t: Significance level of the test

Table 3: Disability, Kinesiophobia and Physical Activity Results

Variable	Women (n=42) X±SD	Men (n=42) X±SD	t	p
Disability score	17.80±7.75	13.80±8.86	2.20	**0.031**
Percentage of disability	36.53±15.75	27.76±17.55	2.41	**0.018**
Kinesiophobia score	44.73±8.53	38.64 ± 8.59	0.26	**0.002**
Physial activity score (MET)	4579.35±6689.15	5600.29±770.48	-0.64	0.518
Physial activity-sittiᵑg score (MET)	299.28±237.28	540.28±348.77	-3.70	**0.000**

Independent Samples t Testi, X: Mean, SD: Standard deviation,p: Statistical Significance, t: Significance level of the test

STATISTICAL ANALYSIS

The sample size was calculated by using the G Power 3.1.9.2 program with an effect value of (d) 0.80, power (1-β) 0.95, and α-value of 0.05, and taking into consideration the means and standard deviations of the distribution of the scores of the subdimensions of the pain avoidance scale by men and women from the previous thesis work, which resulted in the inclusion of 84 individuals (42 male and 42 female). SPSS Statistics 21.0 package program was used. Since the assumptions of parametric tests were met, the Independent Sample t test was used to compare independent group differences. Relationships between continuous variables were examined with Pearson correlation analyses.

RESULTS

A total of 84 (42 female, 42 male) subjects with CLBP were included in the study. The mean age of females was 43.23±8.40 years, and the mean age of males was 37.09±12.16 years. The mean pain duration of women was 63.04±92.90 months, and the mean VAS score was 6.15±1.66 cm. The mean pain duration of men was 46.40±64.03 months, and the mean VAS score was 5.25±2.28 cm. The demographic and clinical data show in Table 1.

In the examination of women's pain management, the mean scores for self-coping were 19.07±7.86, 12.52±4.66 for helplessness, 12.76±5.29 for conscious cognitive intervention, and 12.50±4.93 for seeking medical help. The mean scores for self-coping help in men's pain management were 16.54±7.57, 9.11±4.73 for helplessness, 10.11±5.14 for conscious cognitive intervention, and 10.80±5.26 for seeking medical help. There was a statistically significant difference between women and men with CLBP in the mean scores for helplessness (p=0.001) and conscious cognitive intervention (p=0.023). There was no statistically

Table 4: The Relationship Between Pain Management and Pain Duration, Pain Intensity, Disability, Kinesiophobia, and Physical Activity in Women with Chronic Low Back Pain

Variable	Pain Duraiton	Pain İntensity	Kinesiophobia	Physical Activity	Physical Activity-Sitting	Disability Score	Percentage of Disability
Self-coping	r=-0.206 p= 0.19	r= 0.204 p= 0.195	r= -0.112 p= 0.479	r= -0.096 p= 0.546	r= -0.44 p= 0.781	r= -0.264 p= 0.91	r= -0.211 p= 0.18
Helplessness	r= 0.084 p= 0.595	r= 0.182 p= 0.248	r= 0.426 p= 0.005	r= 0.096 p= 0.544	r= 0.082 p= 0.607	r= 0.397 p= 0.009	r= 0.474 p= 0.002
Conscious cognitive intervention	r= -0.137 p= 0.388	r= -0.005 p= 0.975	r= -0.024 p= 0.880	r= 0.082 p= 0.607	r= -0.019 p= 0.906	r= -0.036 p= 0.823	r= 0.050 p= 0.755
Seeking medical help	r= 0.080 p= 0.612	r= 0.160 p= 0.311	r= 0.308 p= 0.047	r= 0.089 p= 0.573	r= 0.013 p= 0.936	r= 0.197 p= 0.212	r= 0.306 p= 0.049

Pearson Correlation Analysis, p: Statistical Significance, r: Correlation Coefficient

Table 5: The Relationship Between Pain Management and Pain Duration, Pain Intensity, Disability, Kinesiophobia, and Physical Activity in Men with Chronic Low Back Pain

Variable	Pain Duraiton	Pain İntensity	Kinesiophobia	Physical Activity	Physical Activity-Sitting	Disability Score	Percentage of Disability
Self-coping	r=-0.226 p= 0.149	r= -0.060 p= 0.708	r= 0.089 p= 0.574	r= -0.274 p= 0.079	r= -0.077 p= 0.628	r= -0.003 p= 0.984	r= -0.018 p= 0.910
Helplessness	r= 0.121 p= 0.446	r= 0.159 p= 0.313	r= 0.534 P= 0.000	r= -0.512 p= 0.001	r= 0.120 p= 0.449	r= 0.373 p= 0.015	r= 0.362 p= 0.018
Conscious cognitive intervention	r= -0.192 p= 0.222	r= -0.067 p= 0.675	r= 0.213 p= 0.175	r= -0.440 p= 0.004	r= 0.020 p= 0.900	r= 0.101 p= 0.524	r= 0.086 p= 0.589
Seeking medical help	r= 0.044 p= 0.784	r= 0.231 p=0.142	r= -0.094 p= 0.553	r= -0.171 p= 0.278	r= 0.232 p= 0.140	r= 0.252 p= 0.107	r= 0.266 p= 0.089

Pearson Correlation Analysis, p: Statistical Significance, r: Correlation Coefficient

significant difference in the mean scores of self-coping and seeking medical help (p> 0.05) (Table 2).

Statistically significant difference was found between men and women with CLBP in disability score (p = 0.031), percentage of disability (p=0.018), and kinesiophobia score (p=0.002). There was no significant difference in the patients' mean physical activity score (p>0.05), but a significant difference was found in the sitting physical activity level (p<0.01) (Table 3).

When examining the physical activity of individuals with chronic low back pain, it was found that 16 (38%) women were inactive, 14 (33%) women were very active, and 12 (29%) women were minimally active. Among men, 20 (48%) were very active, 12 (28%) were inactive, and 10 (24%) were minimally active.

In women with chronic low back pain, a significant moderarte correlation was found between the subdimension of helplessness in dealing with pain and kinesiophobia (p=0.005), disability score (p=0.009), and percentage of disability (p=0.002). In addition, a significant relationship was found between the subdimension of seeking medical help for pain management and the percentage of kinesiophobia (p=0.047) and disability (p=0.049) (Table 4). There was no statistically significant association between the parameters of self- coping and conscious cognitive interventions and pain duration, pain intensity, kinesiophobia, physical activity score, and disability level (p > 0.05) (Table 4).

In men with chronic low back pain, a significant association was found between the helplessness subdimension in pain management and kinesiophobia (p=0.000), physical activity score (p=0.001), disability score (p=0.015), and disability level (p=0.018). In addition, a significant relationship was found between conscious cognitive attempts and the physical activity score (p=0.004). There was no statistically significant association between the parameters of self-coping and seeing a doctor and pain duration, pain intensity, kinesiophobia, physical activity score, and disability level (p > 0.05) (Table 5).

DISCUSSION

In our study, which aimed to investigate whether the form of pain coping in patients with chronic low back pain differs according to gender, it was found that the scores of women with chronic low back pain for self-coping, helplessness, seeking medical help, and conscious cognitive interventions in their pain coping style were higher than those of men. Although women experience greater feelings of helplessness than men, they perform better on conscious cognitive interventions for pain management. However, there are differences in pain coping styles between men and women; feelings of helplessness in pain coping lead to kinesiophobia in both sexes, which limits physical activity and increases levels of disability.

Meints and Edwards reported that the presence of chronic pain causes not only biological but also cognitive and behavioral problems. They explained that personal factors, social environments, and environmental factors influence a person's attitude toward pain (Meints ve Edwards, 2018). Therefore, individual differences, experiences, and preferences are important in pain

management success. People with chronic pain need different strategies to cope with pain. Pain management has cognitive, emotional, behavioral, and physiological subdimensions (Madenci ve ark., 2006). According to Lazarus, pain coping is a cognitive process of actively selecting coping responses after threat and cause evaluation (Lazarus ve Folkman, 1984). There are different classifications for coping with pain. Active coping refers to controlling the pain or moving despite the pain. Passive coping refers to withdrawing and giving up control due to extreme pain. Similarly, avoidance and fear of pain are defined in the approach to defining pain and examining its causes (Van Damme ve ark., 2008). Bussing et al. reported that individuals with chronic pain who use more self-directed coping methods, such as positive thinking and believing that pain can be relieved, have better physical functioning and higher life satisfaction (Büssing ve ark., 2010).

Karaman et al. examined coping with chronic pain using the Pain Coping Inventory in 97 elderly individuals consisting of 55 women and 42 men. Scores for passive coping (anxiety, calm, and withdrawal) were higher than scores for active coping (disengagement, transformation of pain, and comforting thoughts) in both genders. In terms of gender, they found that women's scores for coping with active and passive pain were higher than men's (Karaman ve ark., 2021). In our study, women were found to have higher scores than men for self-control, helplessness, conscious cognitive interventions, and seeking medical help when coping with pain.

When Crowe et al. examined pain coping in 64 individuals with chronic low back pain, they found that pain self-management with clinical guidelines was the best coping method. Individuals with chronic low back pain were likelier to prefer medication, exercise, and heat applications when self-managing pain (Büssin ve ark., 2010). When Demir Saka and Gozum examined pain selfcare practices in 258 individuals, the most commonly used non-drug self-care practices for pain relief were restriction of rest and activity by 43.4%, applying anything to the painful area by 38.8%, massaging the painful area by 33.7%, and hot water application by 32.6% (Karaman ve ark., 2021). Our study found that the highest pain-coping scores in women and men with chronic low back pain were in self-management. Women's self-management scores were better than men's.

In his study, Kawi examined perceptions of pain management, pain management support, and functional abilities. While people preferred to increase functional activity by using more medication for pain management, they emphasized that they experienced anxiety and fear due to pain and that people with pain should be psychologically supported (Crowe ve ark., 2010). Passive coping strategies such as withdrawal, rest, and medication use in pain management were associated with increased pain, depression, disability, and poor psychological adjustment. Behaviors such as avoiding fear of pain, waiting for a miracle, seeking social support, displaying emotional intolerance, and avoiding moving the painful area are described as maladaptive behaviors (Demir Saka ve Gözüm, 2020; Peres ve Lucchetti, 2010).

Varela and Van Asselt examined the causes of low back pain and disability in 80 individuals aged 20-60 with chronic nonspecific low back pain. It was found that there was a negative relationship between coping with one's pain and level of disability, physical activity, kinesiophobia, and emotional state. It was emphasized that psychosocial factors should be very good for coping with self-pain (Kawi, 2014). Luque Suares et al. reported that kinesiophobia was related to the quality of life, pain intensity, and disability in 10,726 individuals with chronic musculoskeletal pain, and that as kinesiophobia increased, disability scores and pain intensity increased, while the quality of life worsened (Snow-Turek ve ark., 1996). Our study found that disability and kinesiophobia scores were higher, and physical activity scores were lower in women with chronic low back pain than men. Helplessness and seeking medical help for pain management were associated with kinesiophobia and disability scores in both men and women, and their physical activity levels were limited.

CONCLUSION

Pain coping has cognitive, emotional, behavioral, and physiological subdimensions. Therefore, to achieve successful pain management outcomes in individuals with chronic low back pain, multidimensional treatment should be used, including education about pain management, psychological support, and behavioral therapy, in addition to the use of various therapeutic methods to inhibit pain, taking into account individual differences and treatment expectations.

The methods of coping with pain in people with low back pain, their disability levels and their kinesiophobia and physical activity levels have been a subject of research in recent years. Our study is important in terms of showing the reflections of the factors related to low back pain in different genders and explaining whether the

methods of coping with pain differ between genders. The results of our study showed that individuals should be evaluated multidimensionally in terms of biopsychosocial aspects in the management of pain. In order to be successful in coping with pain, individual differences should be taken into consideration.

ETHICAL APPROVAL

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by Pamukkale University Non-Interventional Clinical Research Medical Ethics Committee (Date: 24.12.2019/ No: 22). This study was retrospectively registered at Clinical Trials.gov (ID: NCT06125496).

Informed consent was obtained from all individual participants included in the study.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Nuri Usta, Filiz Altug and Ayse Unal. The first draft of the manuscript was written by Nuri Usta and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

The authors have no relevant financial or non-financial interests to disclose.

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Research Article

Determinants of upper extremity functions in dentists with chronic neck pain

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ABSTRACT

Dentistry is a profession that requires mental and physical attention due to the nature of the work performed. Especially manual dexterity, psychomotor skills and long-term static stay in the same position due to procedures in a small area can disrupt the symmetry of the body and cause neck pain and disability in upper extremity functions over time. The aim of this study was to identify the determinants of upper extremity functions in dentists with chronic neck pain. A total of sixty dentists with chronic neck pain were included in the study. The sociodemographic characteristics of participants were recorded. Right and left upper trapezius pain pressure threshold (PPT), neck disabilities, upper extremity functions of the participants were evaluated by algometry, neck disability index (NPI) and the disabilities of arm, shoulder and hand (DASH), respectively. The mean age of the participants was 35.30±4.16 and the number of women and men was 45 and 15, respectively. A significant relationship was found between DASH and NDI (r=0.449, p=0.009), right trapezius PPT (r=-0.470, p=0.005) and left trapezius PPT (r=-0.354, p=0.043) of the participants. After regression analysis, only NDI was found to be significant as a determinant of upper extremity functions. This can be explained by the fact that disabilities of the proximal parts of the body can be a determining factor in the development of disabilities in the distal parts. In this context, giving these patients exercises that will reduce neck region disability will improve upper extremity functions.

Key words: Dentists, upper extremity functions, chronic neck pain,

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INTRODUCTION

Musculoskeletal disorders (MSD) are a wide range of conditions that affect the tendons, muscles, nerves, ligaments and other tissues of the body. MSD can result from a single event or from cumulative trauma and lead to substantial physical and functional limitations among affected individuals. Among professions in healthcare area, dentists are at high risk of developing occupation-related musculoskeletal problems (Pancholi et al., 2018). Previous studies have indicated that pain and functional limitations are most prevalent in the neck, lower back, shoulder, chest, wrist, knee, elbow, and ankle, respectively (Kawtharani et al., 2023; Ohlendorf et al., 2020).

The Disabilities of the Arm, Shoulder and Hand (DASH) is used to assess upper extremity functions (Hudak et al., 1996). It is a reliable and valid tool to use in patients with chronic neck pain (CNP) (Sigirtmac & Oksuz, 2021). Previous studies have shown that DASH is affected

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by CNP and an increase in disability has been observed in patients with CNP (Osborn & Jull, 2013). A study has assessed the relationship between DASH and NDI in patients with non-specific neck disorders. The correlation was found to be moderate-high ($\rho = 0.669$; $p < 0.001$) (Osborn & Jull, 2013).

The increase in DASH questionnaire points may be associated with pain or neck disability index (NDI). The determination of the predictors of upper extremity functions, and the development of solutions for these predictors, may be beneficial to prevent disabilities and to facilitate daily activities. A study conducted by Mairi Mclean et al. (2011), indicated that upper limb disability was reported by patients with neck pain/disability. However, it has not been studied in dentists with CNP (McLean et al., 2011).

Review of the literature reveals a lack of evidence on this issue. The aim of this study was to investigate the determinants of upper extremity function in dentists with chronic neck pain (CNP).

MATERIAL AND METHODS

Study Design

This study is descriptive research. It was conducted between May 2023 and January 2024. Approval was obtained from the Dokuz Eylul University Ethics Committee for Non-Invasive Research (7681-GOA). Before the study, all participants provided written informed consent.

Participants

A survey was conducted at local clinics and universities to identify dentists with non-specific neck pain, who were subsequently invited to participate in the study through face-to-face interviews. A total of sixty dentists with chronic neck pain volunteered to take part in the study. Individuals with any vascular or neurological disease, a history of upper extremity surgery, or regular participation in exercise or training programs were excluded from participation.

Outcome Variables

Demographic characteristics (gender, age, body mass index (BMI), weight, height) of participants were recorded.

Pain-Pressure Threshold

A Baseline Dolorimeter (Wagner Instruments, Greenwich, CT) was used to assess pain pressure threshold (PPT). The Baseline Dolorimeter has been identified as a valid and reliable instrument to assess PPT and has been successfully used in the evaluation of individuals with neck pain (Ylinen et al., 2005). Measurements were taken from the midpoint of the bilateral upper trapezius muscle while the participants were seated with their knees and hips at 90° of flexion. The measurements were conducted three times for each side, and the mean value was recorded in kg/cm².

The Disabilities of the Arm, Shoulder and Hand Questionnaire

DASH was used to evaluate the functionality of the upper extremities. Validity and reliability of the DASH in Turkish was conducted and is used to evaluate symptoms and functional status in upper extremity musculoskeletal disorders (Düger et al., 2006). The results of the survey were expressed as a number between 0 and 100, with 100 representing the highest level of disability and 0 indicating no disability.

Neck Disability Index

The Neck Disability Index (NDI), a tool designed to assess disability specific to neck pain, was employed for this study. The validity of the NDI in Turkish has been previously established, with an intraclass correlation coefficient (ICC) range of 0.96-0.98 (Aslan et al., 2008). The questionnaire comprises 10 parameters, including pain intensity, personal care, carrying, headache, reading, concentration, working, sleeping, driving and recreational activities. For each parameter, a score of A or 0 is recorded for the absence of disability, while a score of F or 5 is assigned to indicate total disability (Aslan et al., 2008). An increase in the score shows a higher level of disability.

Statistical Analyses

Statistical Package for Social Sciences software (IBM Corporation, version 24.0 for Windows was used to analyze all data. Descriptive statistics were presented as frequencies and percentages for categorical variables, whereas continuous variables were presented as mean and standard deviation. Histograms and Shapiro-Wilk test were used to analyze the normality of the data. Additionally, box plots were employed to ascertain the presence of any outliers. The homogeneity of within-groups variances was analyzed with the M test. The Pearson correlation coefficient was used to investigate correlations between the variables since the data was normally distributed. The correlation coefficient (r) between 0.20 and 0.39 is a weak correlation, between 0.40 and 0.59 is moderate, between 0.60 and 0.79 is strong, and

between 0.80 and 1.0 is a very strong correlation. A multiple linear regression analysis with the enter model was conducted to ascertain the independent variables that exerted the strongest effect on DASH. The significance level was accepted as 0.05 or below.

RESULTS

A total of 60 dentists followed up with CNP were included in our study. Of the dentists, 45 (75%) women and 15 (25%) men and the mean age was 35,30±4,16 years. All the variables are presented in Table 1.

Table 1: Participants' characteristics

	Dentists with CNP (n=60) Mean ± SD %
Age (years)	35.20±4.16
Height (cm)	167.34±7.14
Weight (kg)	66.70±10.58
Gender	
Female	45 (75%)
Male	15 (25%)
BMI (kg/m2)	23.74±2.98
PPT (R)	1.40±0.38
PPT (L)	1.28±0.38
DASH	25.81±15.81
NDI	15.95±3.65

CNP, chronic neck pain, SD, standard deviation, BMI, body mass index, PPT, pain-pressure threshold, DASH, disabilities of arm, shoulder and hand, NDI, neck disability index

According to correlation analyses performed, there was a moderate correlation with NDI (r = 0.449, p= 0.009), right trapezius PPT (r = -0,470, p= 0.005). Additionally, a weak correlation was found with left trapezius PPT (r = 0.374, p= 0.043). There was no significant correlation with age, height, weight or BMI (Table 2).

Both the NDI and PPT measurements were considered in a multiple linear regression enter model. Only the NDI was found to be a determinant of upper extremity functions accounting for 25,9% of the DASH (F=5,928, p=0,006, Table 3).

Table 2. Correlation of upper extremity functions with patients' characteristics

Parameter	DASH	
	r	p
Age (years)	0.011	0.935
Height (cm)	-0.076	0.582
Weight (kg)	-0.057	0.682
PPT (R)	-0.470	0.005
PPT (L)	-0.354	0.043
BMI (kg/m2)	-0.012	0.933
NDI	0.449	0.009

CNP, chronic neck pain, SD, standard deviation, BMI, body mass index, PPT, pain-pressure threshold, DASH, disabilities of arm, shoulder and hand, NDI, neck disability index

Table 3. Determinants of upper extremity functions in dentists with CNP

Parameter	DASH	
	Unstandardized B (95% CI)	p
Constant	22.781 (0.357, 45.205)	-
PPT (R)	-12.395 (-30.554, 5.763)	0.177
PPT (L)	-3.363 (-21.671, 14.946)	0.714
NDI	1.554 (0.463, 2.646)	0.006*

CNP, chronic neck pain, DASH, disabilities of arm, shoulder and hand, PPT, pain-pressure threshold, NDI, neck disability index, *p<0.05 R=0.508, R2=0.259, (F=5,928, p=0,006).

DISCUSSION

The aim was to conduct an investigation into the determinants of upper extremity functions in dentists with CNP. The main results of this study show that NDI and both PPT measurements were correlated with upper extremity functions and NDI is a determinant of upper extremity functions in dentists with CNP.

Dentistry is one of the healthcare professions that inevitably necessitates a combination of mental and

physical attention. In the course of their work, dentists are often obliged to perform tasks in positions that are not ergonomically optimal, whether that be standing or sitting, with rare opportunities for rest (Ohlendorf et al., 2020). Additionally, repetitive and squeezing movements of the arm, wrist and fingers during their work can lead to neurogenic inflammation and increase sensitivity. In addition to these, inadequate lighting, stress and hereditary factors can contribute to the development of various musculoskeletal disorders in dentists (Bhatia et al., 2024). All these reasons lead to contracted upper trapezius muscle and facilitating a chemical sensitization process and leading to a decrease in PPT measurements (Rojas et al., 2021). Moreover, as the time passes, it leads to disabilities in both neck and upper extremity functions. These reasons can explain why both PPT measurements have a negative correlation with DASH. However, after regression analysis PPTs have not been found as a determinant factor of upper extremity functions. Therefore, PPT may not be the direct cause of the disability but a consequence of pain-related factors such as stress, poor sleep as shown in the literature (Rojas et al., 2021).

The available studies indicate that there is a moderate-high positive correlation between NDI and DASH in patients with CNP (Gurav & Panhale, 2017; Osborn & Jull, 2013). Nevertheless, to our knowledge, there is no study that investigated the relationship in dentists with CNP. The results of the present study indicate a positive, moderate correlation between the two variables. After the regression analysis, NDI was found to be a determinant factor for disabilities in upper extremity functions. It has been demonstrated that individuals who adopt a forward head posture as a result of their working conditions can experience a reduction in the activation of the stabilizing muscles in the neck area, which may subsequently lead to a loss of strength over time (Çobanoğlu et al., 2024). The loss of strength causes deterioration in stabilization and therefore the natural appearance of the spine, causing neck pain (Çobanoğlu et al., 2024). As a result of strains and sprains from overexertion or bad posture, disabilities of shoulder and other upper extremities start to increase. This can be explained by the fact that disabilities of the proximal parts of the body can be a determining factor in the development of disabilities in the distal parts.

It should be noted that the set is derived from a single-city sample, which limits the generalizability of the findings. A further limitation of the study is that the duration and intensity of the pain experienced by the participants could not be assessed.

This is the pioneering study to examine the interrelationships between pain sensitivity, NDI and DASH in dentists with CNP. The utilisation of an objective methodology for the assessment of pain represents a further strength of this study.

In conclusion, DASH was found to be correlated with NDI and bilateral upper trapezius muscles' PPT. The NDI score was identified as a significant predictor of DASH. Future studies should focus on reducing neck disability and improving upper extremity function in dentists with chronic neck pain.

ETHICAL APPROVAL

Approval was obtained from the Dokuz Eylul University Ethics Committee for Non-Invasive Research (7681-GOA).

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Research Article

Amantadine preserve VCAM immunoexpression levels in cardiac injury induced by brain trauma with its anti-inflammatory action and protective effect on the mitochondrial membrane

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ABSTRACT

Brain trauma-induced cytokine storms can impact multiple organs, particularly the heart, through inflammatory and apoptotic mechanisms. This study aimed to examine cardiac pathology following experimental brain trauma (BTCI) and evaluate the protective effects of amantadine (AMN), an NMDA receptor antagonist, on cardiotoxicity. Forty rats were divided into four groups: sham, BTCI, BTCI+AMN-1 (45 mg/kg, ip), and BTCI+AMN-7. Trauma (0.2 Newton) was induced by dropping a 50 g ball from 80 cm. Heart samples were collected 24 hours and seven days post-trauma for histopathological and immunohistochemical analysis. The BTCI group showed hyperemia, hemorrhage, inflammatory infiltrations, increased Bax and VCAM expressions, and decreased Bcl-2 expression. AMN treatment reversed these findings, with greater efficacy observed after seven days. In conclusion, BTCI induces cardiac damage, while AMN provides protective effects. Further studies are needed to clarify underlying mechanisms.

Key words: Brain trauma, heart, VCAM, Bax, Bcl2, inflammation

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INTRODUCTION

In brain trauma caused by various reasons, there is a large amount of cytokine production and release in the tissue as a result of damage to the skull base. It has been proven that these cytokines mixed with the blood can also cause damage to peripheral organs through the permeability of the blood-brain barrier (Cardona et al., 2003; Wilson et al., 2010; Gyoneva and Ransohoff, 2015). Chemokines are released by injured neuronal tissue after brain injury, drawing immune cells to the area of harm. Different cellular processes may be involved in the ensuing inflammatory response, depending on the kind of insult—traumatic contusion, diffuse damage, or elevated intracranial pressure. Experimental trauma studies have shown that in injured areas, neutrophil infiltration occurs first, peaking within a few days. Following this, astrocytes, lymphocytes, and microglia/macrophages migrate to the site of injury (Cardona et al., 2003; Wilson et al., 2010; Gyoneva and Ransohoff, 2015; Alam et al., 2020). It is known that the heart tissue, which is responsible for the blood supply of the whole body, is also affected by this damage, which can indirectly cause an imbalance in the oxygenation of the organs and deepen the damage (Morganti-Kossman et al., 1997; Cardona et al., 2003; Wilson et al., 2010; Gyoneva and Ransohoff, 2015; Alam et al., 2020).

Over the past 20 years, studies in humans have reported that cardiovascular complications have become

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more widespread after brain injury and are associated with increased morbidity and mortality. Hypertension, hypotension, cardiac arrhythmias, ECG abnormalities, the production of biomarkers of cardiac damage, and left ventricular dysfunction are among the range of abnormalities (Zygun, 2005; van der Bilt et al., 2009; Mueller et al., 2020; Huang et al., 2023; Coppalini et al., 2024). In order for cytokines circulating in the blood to affect and penetrate tissues, the synthesis of vascular cell adhesion molecules (VCAM) in the endothelial layer increases. It is known that cytokines that adhere to tissues via these molecules trigger damage, primarily inflammation, in the tissue and also affect apoptotic processes. VCAM-1 has been reported to be an important biomarker in cardiovascular diseases (Troncoso et al,.2021). It has been proven that apoptosis occurring in cardiac tissue can cause losses at the cellular level, leading to deterioration in functions and indirectly in the vascularization of distant organs. It has been shown that in the event of damage to mitochondria, which are responsible for energy and respiration at the cellular level within the cell, B-cell lymphoma 2 (BCL-2) and Bcl-2-associated X protein (BAX) levels are disrupted, causing apoptosis (Bennett, 2002; Elmore 2007).

It is known that amantadine has antiviral effects against influenza A virus, reduces cytotoxicity with its N-methyl-D-aspartate (NMDA) receptor antagonist effect, and causes dopamine discharge in the treatment of parkinsonism. It has been shown in a limited number of studies to have anti-inflammatory and antiapoptotic effects (Jiménez-Jiménez et al., 2020; Dekundy, et al., 2024).

Publications reporting cardiac manifestations following brain trauma have rapidly increased in recent years. However, experimental studies and explanations regarding the pathogenetic mechanisms remain quite limited. The aim of this study is to investigate the pathological and immunohistochemical changes occurring in the heart after experimental brain trauma (BTCI), and to explore the effects of amantadine on VCAM/BCL2 and BAX expressions in its potential protective role against cardiac damage induced by brain trauma. The potential action mechanism of brain trauma induced heart injury is shown in Figure 1.

MATERIAL AND METHODS

Animals and ethical approval

All experimental processes applied in the study was performed following the guidelines for animal research outlined by the Animal Research: Reporting In Vivo Experiments (ARRIVE) 2.0 and were approved by the Committee on Animal Research at Süleyman Demirel University (approval no: 392). Furthermore, support for the study was provided by the Süleyman Demirel University Scientific Research Project Unit (SDU-BAP) under the project number TSG-2023-9092. During the trials, the animals from Süleyman Demirel University's Animal Experiments Laboratory were kept at 21–22°C, 60% ± 5% humidity, and a 12-hour light–12-hour dark cycle. They were also given water and standard commercial feed as needed.

Creation of trauma model

In order to create a brain trauma model, the impact acceleration model made by Marmarou et al. by dropping a 50 mg ball from a height of 80 cm was used. Thus, it was aimed to create a trauma of 0.2 N severity according to Newton's law (Marmarou et al., 1994)

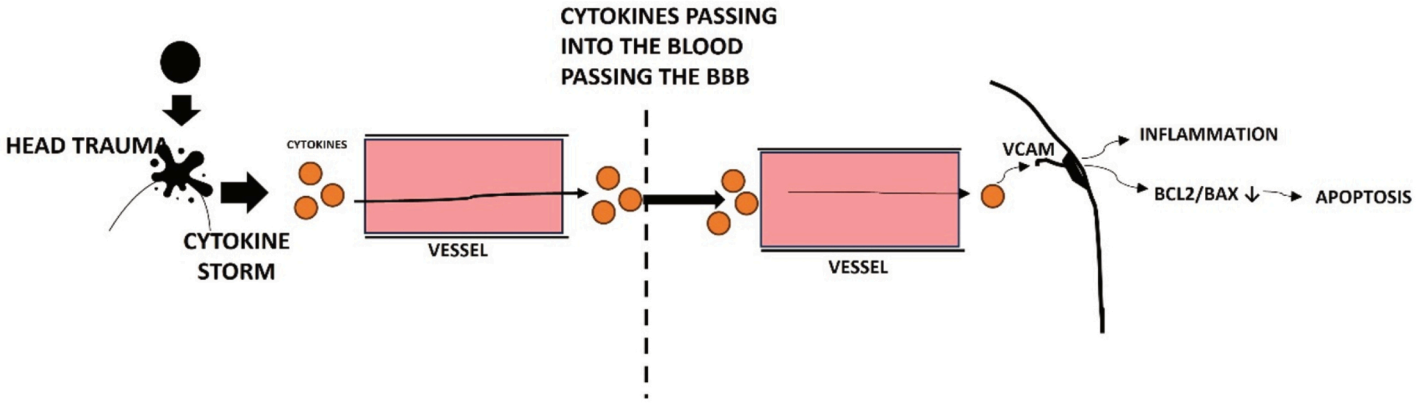

Figure 1. Potential pathological mechanism of brain trauma induced cardiac injury
VCAM: Vascular cell adhesion molecules, BCL2: B-cell lymphoma 2, BAX: Bcl-2-associated X protein

STUDY DESIGN

Totally, weighing 300-350 grams forty Wistar Albino male were divided into four groups. Groups were;

- Sham group: Incision was made and trauma was not induced. Then 0.5-1 ml of physiological serum (SF) were administered intraperitoneally (ip). After 24 hours, rats sacrificed under anesthesia and heart tissues were taken.
- BTCI group: Incision were made, trauma was created and then 0.5-1 ml of SF administered ip. After 24 hours, rats sacrificed under anesthesia and heart tissues were taken.
- BTCI+AMN-1: Incision were made, trauma was created and then 0.5-1 ml 45 mg/kg AMN were administered ip (Hardeland et al., 2010; Orhan et al., 2021). After 24 hours, rats were sacrificed under anesthesia and heart tissues were taken.
- BTCI+AMN-7: Incision were made, trauma was created and then 45 mg/kg AMN were administered ip once a day for 7 days. After the 7th day, the rats sacrificed under anesthesia and their heart tissues were taken.

For all experimental procedures 80-90 mg/kg ketamine (Ketalar, Pfizer, Türkiye) and 8-10 mg/kg xylazine (Xylazinbio %2, Bioveta, Czech Republic) were used for anesthesia. A surgical exsanguination was performed by taking blood from the inferior vena cava for the sacrification process. Blood samples and heart tissue were taken and fixed in formaldehyde solution for histopathological and immunohistochemical examinations.

Histopathological Method

Heart samples were taken during necropsy and fixed in a 10% neutral formalin solution. Afterwards, the samples were embedded in paraffin wax using a standard tissue processing method employing a fully automated tissue processing device (Leica ASP300S, Wetzlar, Germany). Subsequently, 5 µm thick sections were sliced from the paraffin blocks using a fully automated rotary microtome (Leica RM2155, Leica Microsystems, Wetzlar, Germany). These sections were then stained with hematoxylin-eosin (HE), covered, and examined under light microscopy.

Histological lesions in the hearts were assessed semi-quantitatively using an ordinal grading system. This assessment involved evaluating hyperemia, hemorrhage, inflammatory cell infiltrations, and degenerative necrotic changes in myocardial cells. Descriptions of normal (score = 0), mild (score = 1), moderate (score = 2), and severe (score = 3) affections were assigned scores ranging from 0 to 3 (Table 1).

Table 1: Histopathology score of hepatic lesions

	Severity	Description	Score
Histopathological changes	Normal		0
	Mild	< 3 foci	1
	Marked	4-6 foci	2
	Severe	> 7 foci	3

Immunohistochemical examination

Three sets of slices were cut from the paraffin blocks and placed on poly-L-lysine-coated slides for immunohistochemical examination. Following the manufacturer's instructions, sections were then immunohistochemically stained using the streptavidin-biotin method to evaluate the expression of Bax (Recombinant Anti-Bax antibody [E63] (ab32503)), Bcl-2 (Anti-Bcl-2 antibody (ab194583)), and VCAM (Recombinant Anti-VCAM1 antibody [EPR5047] (ab134047)). Abcam (Cambridge, UK) supplied the primary antibodies, which were utilized at a dilution of 1/100. The sections were incubated with the primary antibodies for 60 minutes before being subjected to immunohistochemistry using a biotinylated secondary antibody and a streptavidin-alkaline phosphatase conjugate. The chromogen was diaminobenzidine (DAB), and the secondary antibody was the Mouse and Rabbit Specific HRP/DAB IHC Detection Kit-micro-polymer (ab236466) from Abcam (Cambridge, UK). Primary antibodies were substituted with antigen dilution solution for negative controls. A qualified pathologist from a different university performed each evaluation on blinded samples.

At an objective magnification of X40, the IHC expressions were scored on a scale of 0-3. Accordingly, 0 indicates no expression, 1 indicates focal and weak staining, 2 indicates diffuse and weak staining, and 3 indicates diffuse and marked staining (Table 2). The Image J 1.48 software (National Institutes of Health, Bethesda MD) was used to determine the positive

reaction. An Olympus CX41 model microscope was used for photographing the results, and the Database Manual Cell Sens Life Science Imaging Software System

(Olympus Corporation, Tokyo, Japan) was used for microphotography.

Table 2: Immunohistochemical score of cardiac biomarkers

Immunohistochemistry expressions	Focal and weak staining	1
	Diffuse and weak staining	2
	Diffuse and marked staining	3

Statistical Analysis

We utilized Graphpad Prism 10 (Version 10.1.0) (GraphPad Software, USA) for statistical analysis. The Shapiro-Wilk test was first used to examine the data for normality of distribution. One-way analysis of variance (ANOVA) was used to compare the groups because the data displayed a normal distribution (P>0.05). Group differences were determined using the Tukey test, with P < 0.05 being regarded as statistically significant. The Mann-Whitney U test and Dunnett's C test were employed to identify group differences in nonparametric data.

RESULTS

Histopathological findings

Microscopic examination revealed no pathological changes in the myocardial tissue of the control group. Cardiomyocytes in this groups appeared elongated, branching, and of normal size with well-defined intercalated discs. Delicate endomysium sheaths surrounding the cardiac cells were observed, along with a dense capillary network surrounding the cells. In contrast, the BTCI group exhibited alterations in cardiac tissue, including hyperemia, hemorrhage, and inflammatory cell infiltrations. Degenerative changes characterized by an eosinophilic appearance were observed in cardiomyocytes. Treatment with AMN resulted in the amelioration of these pathological findings. Seven days of treatment were more effective than one day of treatment (Figure 1).

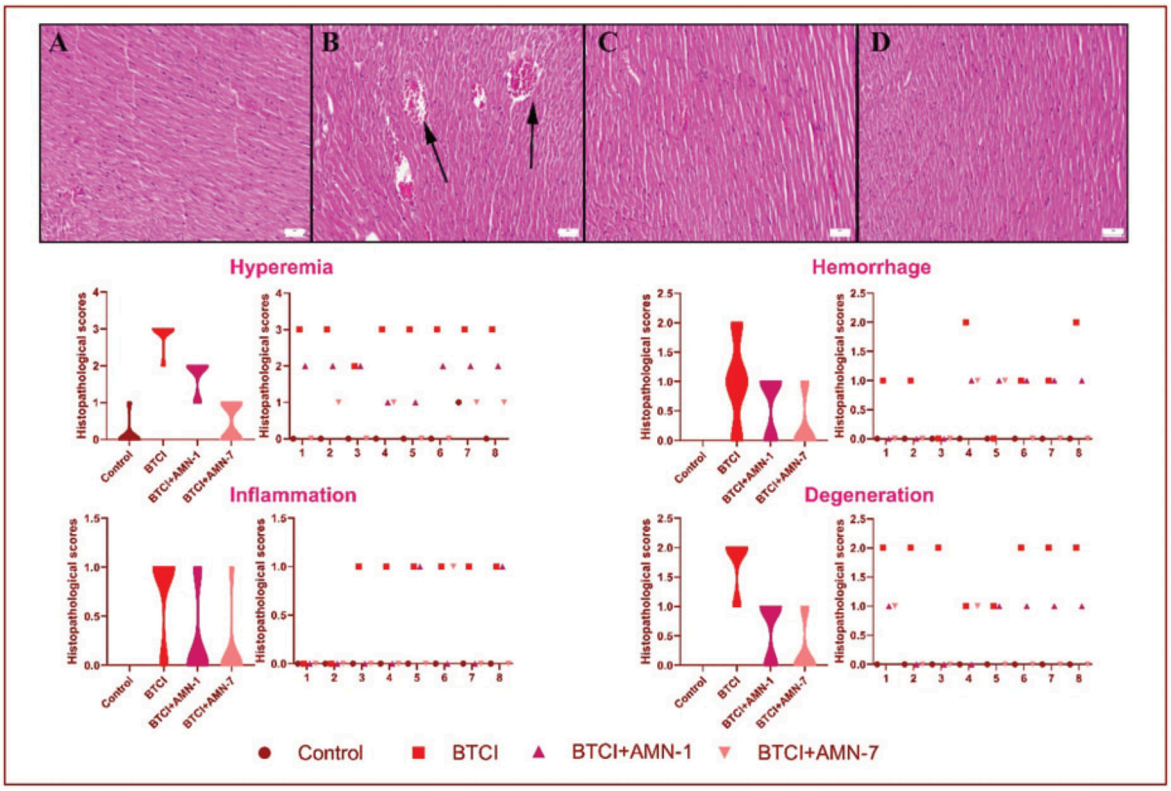

Figure 1: Representative histopathological images of hearts across the groups. (A) Normal myocardial tissue histology in the control group, (B) Severe hyperemia (arrows) in the BTCI group, (C) Marked amelioration in pathological changes in the BTCI+AMN-1-day group, (D) Normal myocardium histology in the BTCI+AMN 7-day group, E, scale bars=20µm. BTCI: Brain trauma induced cardiac injury, AMN: Amantadine, Values are represented as means ± SD, p≤0.001.

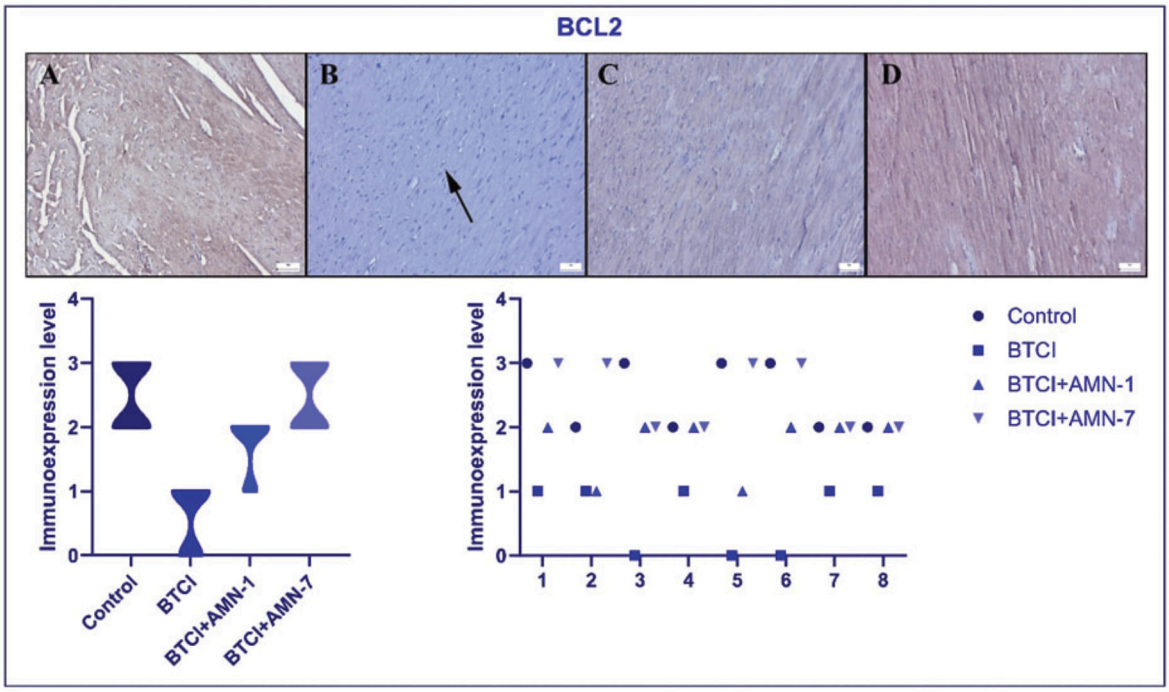

Figure 2. Immunohistochemical expressions of Bcl-2 in the hearts across the groups. (A) Marked Bcl-2 expression in the control group. (B) Decreased Bcl-2 expression in myocardial cells (arrows) in the BTCI group. (C) Moderately increased Bcl-2 expression in the BTCI+AMN-1-day group. (D) Marked Bcl-2 expression in the BTCI-AMN-7-day group, Streptavidin biotin peroxidase method, scale bars = 20 μm. Bcl-2: B-Cell Lymphoma 2, BTCI: Brain trauma induced cardiac injury, AMN: Amantadine, Values are represented as means ± SD, p≤0.001.

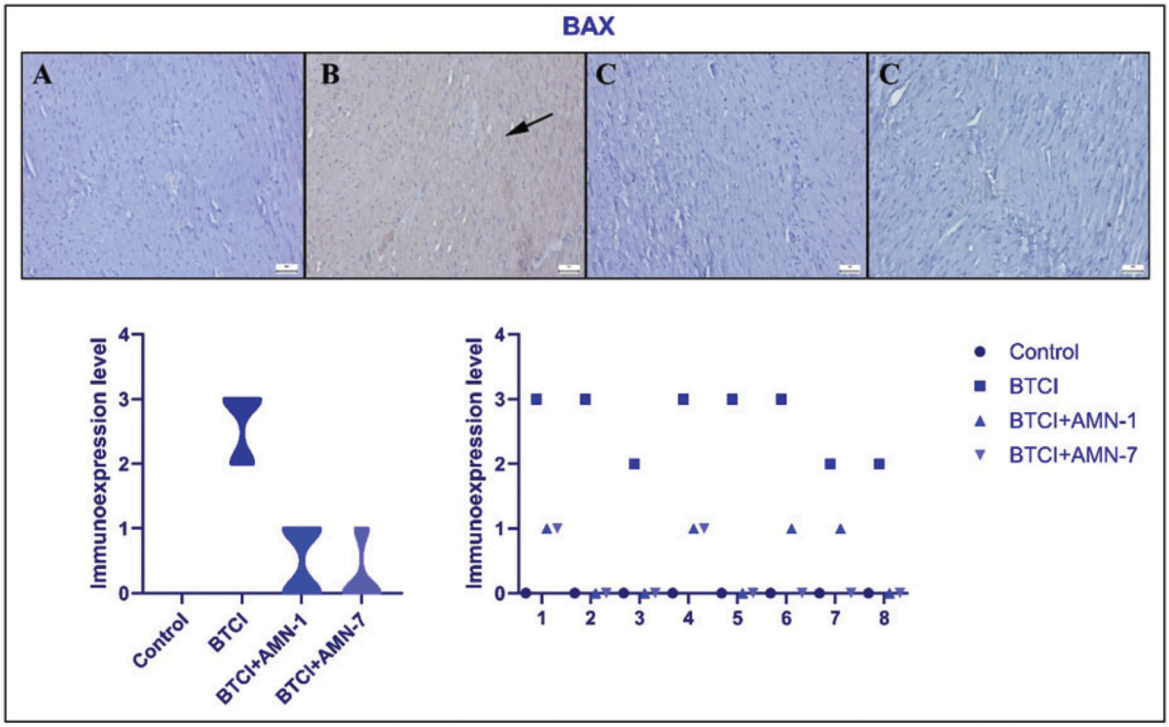

Figure 3. Immunohistochemical expressions of Bax in the hearts across the groups. (A) Negative Bax expression in the control group. (B) Increased Bax expression in myocardial cells (arrows) in the BTCI group. (C) Markedly decreased Bax expression in the BTCI+AMN-1-day group. (D) Negative Bax in the BTCI-AMN-7-day group, Streptavidin biotin peroxidase method, scale bars = 20 μm. Bax: Bcl-2-Associated X Protein, BTCI: Brain trauma induced cardiac injury, AMN: Amantadine, Values are represented as means ± SD, p≤0.001.

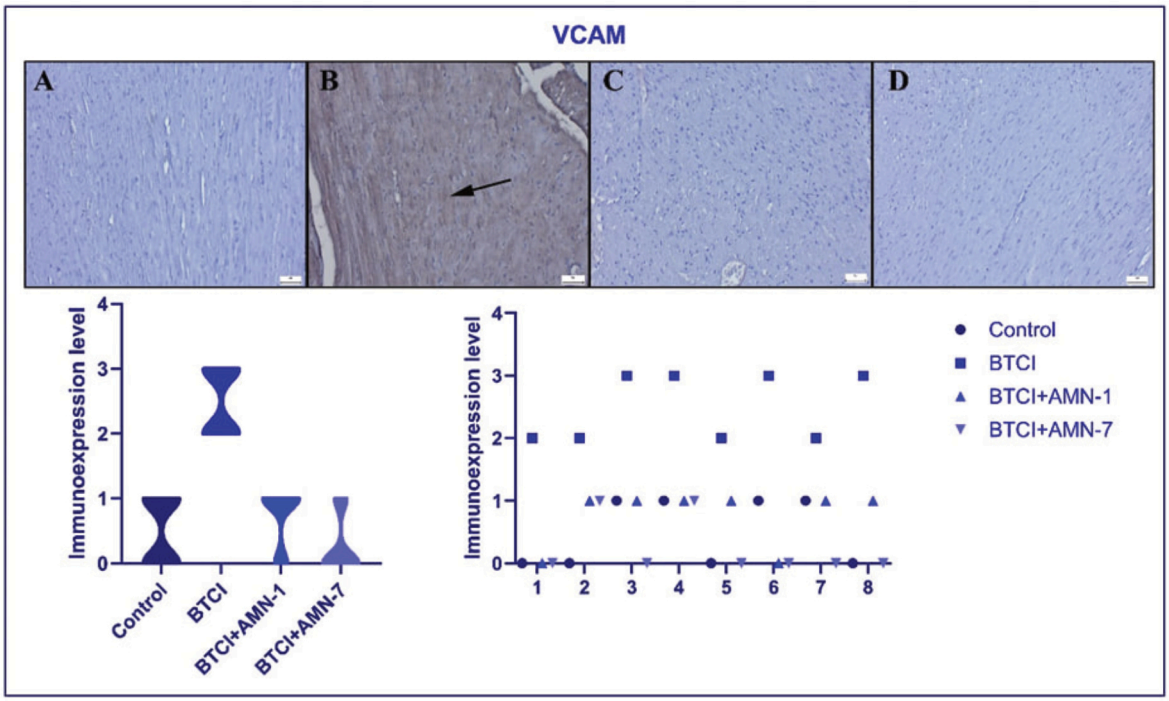

Figure 4. Immunohistochemical expressions of VCAM in the hearts across the groups. (A) Negative VCAM expression in the control group. (B) Increased VCAM expression in myocardial cells (arrows) in the BTCI group. (C) Markedly decreased VCAM expression in the BTCI+AMN-1-day group. (D) Negative VCAM expression in the BTCI-AMN-7-day group, Streptavidin biotin peroxidase method, scale bars = 20 µm. VCAM: Vascular cell adhesion molecule, BTCI: Brain trauma induced cardiac injury, AMN: Amantadine, Values are represented as means ± SD. *p≤0.05, **p≤0.01, ***p≤0.001.)

Immunohistochemical examination

Immunohistochemical investigations revealed very low or non-existent expression of Bax and VCAM but marked expression of Bcl-2 in the control group. Conversely, myocardial cells in the BTCI group exhibited moderate to markedly increased expressions of Bax and VCAM, along with decreased Bcl-2 expressions. Treatment with AMN reversed these pathological findings. Seven days of treatment were more effective than one day of treatment (Fig. 2-4).

DISCUSSION

In this study, heart damage resulting from brain trauma was experimentally demonstrated in a rodent model. Histopathological and immunohistochemical changes in the heart were assessed to explain the mechanism of heart damage. The study results revealed that following brain trauma, both apoptotic and inflammatory activity increased in the heart, leading to myocardial damage. It was also shown for the first time that AMN reduced this damage and could potentially be used in cases of brain trauma.

It is known that traumas occurring in the human body for many reasons can cause distant organ damage in addition to the parts exposed to the trauma (Rachfalska et al., 2020). For this reason, multiorgan damages that occur are fatal and often require intensive care conditions (Cole et al., 2020; Ting et al., 2023). Basic agents used in intensive care conditions may also be insufficient in the treatment of these multiple damages (Abdelbaky et al., 2024). In this study, acute and chronic applications of AMN were effective in reducing the damage in cardiac damage secondary to brain trauma in experimental animals. Although brain trauma seems to be localized to the damage site, distant organ damage can occur due to the inflammatory picture caused by cytokines released from the damaged area into the blood, passing to the peripheral compartment and reaching other tissues. Inflammatory cytokines circulating in the vessel can trigger damage in those areas by binding to their own receptors in the vascular endothelium and heart tissue (Rachfalska et al., 2020). In parallel with this situation, molecules such as VCAM must be present and their expressions must increase in order for inflammatory cytokines to pass to

tissues outside the vessel such as the heart (Kong et al., 2018). In this study, the increase in VCAM expression in the BTCI group with damage to the heart tissue after the brain trauma model supports this situation. In histopathological analyses, the findings of ligated, branching, and of normal size with well-defined intercalated discs, delicate endomysium sheaths surrounding the cardiac cells and dense capillary network surrounding the cells detected in normal heart tissues were replaced by hyperemia, hemorrhage, inflammatory cell infiltrations and degeneration in the BTCI group. The parallelism of these findings with the increase in VCAM expression supports the above-mentioned situations. The regression of all findings with 1-day and 1-week AMN treatment shows that AMN has an anti-inflammatory effect.

Inflammation can often be seen together with apoptosis. For example, it is known that tumor necrosis factor alpha, an indicator of acute inflammation, can trigger apoptosis by directly stimulating caspase-8 mediated caspase-3 by stimulating its receptors on the cell surface, while on the other hand, it can cause damage to the mitochondrial organelle and increase caspase-9 mediated caspase-3 expressions and stimulate apoptosis (Alvarez et al., 2011; McIlwain et al., 2013). Stress, which occurs as a result of damage to the mitochondria, which are responsible for the cell's energy metabolism, causes apoptosis by causing membrane permeability and cytochrome-c release (Guo et al., 2003; Khan et al., 2022; Zong et al., 2024). It is also known that increases in the apoptotic BAX gene found in the membrane are important in cytochrome-c release (Zhang et al., 2017; Garrido et al., 2006). Decreases in this proapoptotic gene with AMN treatment show that apoptosis secondary to inflammation can be regressed by AMN. On the other hand, a decrease in the expression of the BCL gene, which is also an indicator of membrane damage but an antiapoptotic gene, can also trigger apoptosis. The reversal of the decrease in BCL-2 gene expression in the injury groups by AMN shows that the drug has an antiapoptotic attitude (Qian et al., 2022; Öcal et al., 2022).

The limitation of this study is the lack of biochemical and genetic examinations. The primary limitation of this study is the absence of biochemical and genetic analyses. However, this pioneering experimental study has provided valuable insights into the structural and cellular changes in the heart following brain trauma through histopathological and immunohistochemical evaluations.

This study highlights the significant histopathological and immunohistochemical changes in the heart following brain trauma, including increased apoptotic activity and inflammatory responses, which contribute to myocardial damage. The identification of these key mechanisms provides a clearer understanding of the heart's vulnerability to secondary injury post-trauma. Notably, amantadine treatment was shown to effectively reduce both apoptotic and inflammatory markers, indicating its potential as a therapeutic intervention in mitigating myocardial damage in brain trauma cases. These findings underscore the importance of further investigating amantadine's cardioprotective effects in clinical settings.

ETHICAL APPROVAL

All experimental processes applied in the study was performed following the guidelines for animal research outlined by the Animal Research: Reporting In Vivo Experiments (ARRIVE) 2.0 and were approved by the Committee on Animal Research at Süleyman Demirel University (approval no: 392). Furthermore, support for the study was provided by the Süleyman Demirel University Scientific Research Project Unit (SDU-BAP) under the project number TSG-2023-9092. During the trials, the animals from Süleyman Demirel University's Animal Experiments Laboratory were kept at 21–22°C, 60% ± 5% humidity, and a 12-hour light–12-hour dark cycle. They were also given water and standard commercial feed as needed.

ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST

There is no conflict of interest.

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Research Article

Targeting Vaccine Hesitancy: A Data-Driven Approach Using AI and Public Health Data

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ABSTRACT

This study examines H1N1 and seasonal flu vaccination behaviors using machine learning models and explainable artificial intelligence (XAI) techniques. Utilizing data from the National 2009 H1N1 Influenza Survey, we developed a predictive framework employing models such as CatBoost, XGBoost, and LightGBM. CatBoost outperformed others with an accuracy of 0.696 and an F1 score of 0.688. SHAP (Shapley Additive Explanations) was used for interpretability, providing both global insights, such as the critical role of doctor recommendations, and local insights, highlighting individual decision factors. Our findings underscore the importance of addressing vaccine skepticism and improving healthcare communication to enhance vaccination uptake. These results contribute to public health strategies aimed at increasing immunization coverage and preparing for future pandemics.

Key words: Vaccine hesitancy, Healthcare communication, Machine learning, Explainable AI, One health, Public health

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INTRODUCTION

Vaccination remains one of the most effective public health measures to prevent infectious diseases and reduce morbidity and mortality globally. Despite its proven efficacy, vaccine hesitancy continues to pose significant challenges in achieving widespread immunization coverage (Larson et al., 2014). Understanding the factors driving vaccine hesitancy is critical for designing targeted interventions and improving vaccination uptake (Lincoln et al., 2022). This study focuses on predicting vaccination behavior for H1N1 and seasonal flu vaccines, leveraging machine learning models and explainable artificial intelligence (XAI) techniques to provide both predictive accuracy and transparency.

The emergence of the H1N1 influenza virus in 2009 highlighted the urgent need for effective vaccination campaigns to control pandemics. It is estimated that between 151,000 to 575,000 deaths occurred globally within the first year of the outbreak (Harding & Heaton, 2018). Despite the rapid development and deployment of the H1N1 vaccine, vaccine uptake was hindered by factors such as public distrust, misinformation, and logistical barriers (Ayachit et al., 2020). Similar challenges persist with seasonal influenza, as rapid antigenic drift necessitates annual updates to vaccine formulations, complicating public health efforts to achieve adequate coverage (Harding & Heaton, 2018).

The One Health perspective, emphasizing the interconnectedness of human, animal, and environmental health, is particularly relevant in understanding the dynamics of influenza pandemics like H1N1. Influenza A viruses, which can circulate between humans, swine, and avian hosts, are a significant zoonotic threat, as demonstrated by the 2009 H1N1 pandemic (Pappaioanou & Gramer, 2010). The ability of these viruses to undergo genetic reassortment across species underscores the critical need for integrated surveillance systems and collaborative efforts in pandemic preparedness (Kim,

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2018). Additionally, mislabeling such events as "swine flu" during the pandemic led to significant economic consequences for the pork industry, further highlighting the necessity for accurate communication and intersectoral cooperation (Pappaioanou & Gramer, 2010). Vaccination, both in humans and animals, plays a crucial role in mitigating these risks. For instance, efforts to control avian influenza through poultry vaccination and enhanced biosecurity measures have proven essential in preventing spillovers into human populations (Kim, 2018). The One Health framework supports these integrative strategies, advocating for collaborative research and policymaking to address zoonotic disease risks comprehensively (Monath, 2013).

Machine learning (ML) techniques have emerged as powerful tools to predict vaccination behavior by analyzing large datasets with complex, multidimensional variables. Studies have demonstrated the effectiveness of ensemble models like CatBoost and XGBoost in capturing critical predictors of vaccine hesitancy, including socioeconomic, demographic, and behavioral factors (Altarawneh, 2023; Ahmed et al., 2022). Additionally, SHAP (Shapley Additive Explanations) has been widely used to enhance the interpretability of these models, providing actionable insights for public health stakeholders (Lundberg & Lee, 2017).

Recent advancements in ML and XAI have enabled a deeper understanding of vaccine hesitancy, highlighting the role of trust, socioeconomic factors, and cultural perceptions in shaping individual decisions (Ebulue et al., 2024; Alharbi et al., 2024). For instance, studies have shown that lack of trust in government and healthcare institutions significantly correlates with lower vaccination rates (Lincoln et al., 2022). Moreover, the influence of socioeconomic factors, such as income and education, underscores the need for equitable access to vaccination resources, particularly in underserved populations (Ebulue et al., 2024).

This study contributes to the growing body of literature by employing a new and robust methodological framework that integrates predictive modeling with interpretability. By analyzing data from the National 2009 H1N1 Influenza Survey, we aim to identify key factors influencing vaccination decisions and provide a transparent understanding of model predictions. The findings are expected to inform strategies for improving vaccine uptake and addressing barriers to immunization, ensuring better preparedness for future public health crises.

MATERIAL AND METHODS

Study Design and Ethical Statement

This study is a secondary data analysis utilizing the publicly available National 2009 H1N1 Influenza Survey dataset (CDC, 2012), which was conducted to assess public attitudes, behaviors, and vaccination uptake during the H1N1 pandemic. The study employs a mixed-methods approach, integrating machine learning techniques with explainable artificial intelligence (XAI) methods to predict and interpret vaccination behaviors. The target variable is formulated as a 3-class classification system, representing "No vaccination received," "Single vaccination" and "Double vaccination." (“Single vaccination” means patient got just one of the vaccines.) The dataset used in this study is anonymized and publicly accessible, ensuring compliance with ethical standards for secondary data analysis. Since the data does not include identifiable personal information, ethical approval was not required for its use. The principles of the Declaration of Helsinki were adhered to throughout the research, ensuring respect for the autonomy and confidentiality of respondents.

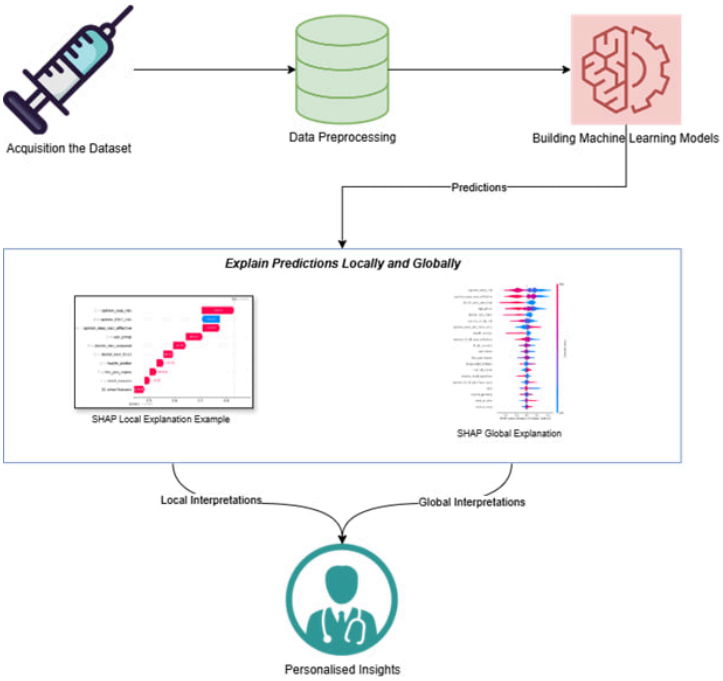

Figure 1: Framework for Generating Predictions and Interpreting Model Explanations

The methodological workflow for predicting and interpreting vaccination behavior is shown in the flowchart (Figure 1). The process begins with dataset acquisition, including features like demographics, opinions on vaccine effectiveness, risks, and doctor recommendations. After preprocessing to handle missing values, encode categorical variables, and remove irrelevant features, predictive models classify vaccination status into three categories: No vaccination, Single vaccination, and Double vaccination. Interpretability is enhanced with SHAP, providing local insights through waterfall plots for individual predictions and global explanations via summary plots to rank feature importance. This transparent framework aids public health officials in designing informed vaccination strategies.

Details of the Dataset

The dataset used in this study originates from the National 2009 H1N1 Flu Survey, conducted during late 2009 and early 2010. This large-scale survey was designed to assess public vaccination behaviors and attitudes in response to the H1N1 pandemic and seasonal influenza. The dataset provides critical insights into vaccination decisions, including demographic, socio-economic, behavioral, and health-related factors influencing individual vaccination outcomes.

The dataset comprises 36 columns and a multi-label target variable, reformulated as a 3-class classification structure for this study. The target variable combines information on two separate vaccination statuses—H1N1 vaccine and seasonal flu vaccine—into three categories:

- 0: No vaccination received
- 1: Single vaccination (either H1N1 or seasonal flu vaccine).
- 2: Double vaccination (both H1N1 and seasonal flu vaccines).

Each row corresponds to a unique respondent, identified by a respondent_id column, and includes 35 additional features capturing demographic, behavioral, and opinion-based data (Table 1).

Feature Engineering

Feature engineering was a critical step in preparing the dataset for machine learning. Missing values were addressed by replacing continuous variables with column means and filling categorical features with "No Category." Key categorical variables, such as age_group and education, were label-encoded, while non-informative columns like respondent_id and employment_occupation were removed to reduce noise. Feature selection combined domain expertise with statistical methods, including Random Forest for feature importance analysis and PCA for exploratory purposes. The refined dataset included demographic, behavioral, health-related, and opinion-based variables, offering a comprehensive foundation for modeling vaccination behavior.

Machine Learning Models

To predict vaccination status, the dataset was modeled as a 3-class classification problem with target labels representing no vaccination, single vaccination, and double vaccination. The following machine learning models were evaluated for their predictive performance:

- Random Forest Classifier: By aggregating the output of individual decision trees, the Random Forest Classifier combines several decision trees to get high accuracy. This paradigm works especially well with complicated data structures. Studies by Putri et al., (2021) and Qorib et al.(2023) demonstrate its success across different fields.
- K-Nearest Neighbors (KNN): A data point's class is predicted by the KNN model using the majority class of its closest neighbors. Studies by Suprayogi et al. (2022), Goswami & Sebastian (2022), demonstrate how well KNN works with a variety of datasets.
- XGBoost: XGBoost, which is well-known for its speed and effectiveness, builds a potent classifier by applying gradient boosting to decision trees. Studies by Cheong et al. (2021), and Nikhil et al.(2024) demonstrate the efficacy of XGBoost in a range of applications.
- LightGBM: Using a tree-based gradient boosting algorithm, LightGBM provides quick training and memory efficiency, making it ideal for huge datasets. Its scalability and efficiency on huge data are highlighted in studies by Ing et al. (2021), Gupta & Verma (2023).
- Support Vector Machine (SVM): To divide data points for classification, SVM creates a hyperplane that maximizes the margin between classes. It is frequently employed for assignments that call for a clear division of classes. The efficacy of SVM on a variety of datasets is demonstrated by studies by, To et al. (2021), and Du et al. (2017).
- CatBoost: Using a gradient boosting technique based on decision trees, CatBoost is made to effectively

handle category features. CatBoost's versatility for categorical data is demonstrated in studies by Ayachit et al. (2020), and Kim (2021).

We used accuracy, recall, precision, and F1 score as evaluation criteria to evaluate each model's performance. Every statistic offers a different viewpoint on how well the model predicts the likelihood of pet adoption.

Table 1: Vaccine Dataset Feature Descriptions

Demographic Features
- age_group: Respondent's age group.
- education: Education level.
- race: Race of the respondent.
- sex: Gender.
- income_poverty: Household income relative to the 2008 Census poverty thresholds.
- marital_status: Marital status.
- rent_or_own: Housing situation.
- employment_status: Employment status.
- hhs_geo_region: Geographic region defined by the U.S. Dept. of Health and Human Services.
- census_msa: Metropolitan statistical area classification.
- employment_industry: Employment industry (categorical).
- employment_occupation: Employment occupation (categorical).

Health-Related Factor Features:
- chronic_med_condition: Presence of chronic medical conditions.
- child_under_6_months: Regular close contact with children under six months.
- health_worker: Healthcare worker status.
- health_insurance: Health insurance status.

Behavioral Factors:
- behavioral_wash_hands: Frequently washed hands or used hand sanitizer.
- behavioral_large_gatherings: Reduced time at large gatherings.
- behavioral_antiviral_meds: Usage of antiviral medications.
- behavioral_avoidance: Avoided close contact with individuals showing flu-like symptoms.
- behavioral_face_mask: Purchased face masks.
- behavioral_outside_home: Reduced contact with people outside their household.
- behavioral_touch_face: Avoided touching eyes, nose, or mouth.

Opinions and Perceptions:
- h1n1_concern: Level of concern about H1N1 flu (0-3 scale).
- h1n1_knowledge: Level of knowledge about H1N1 flu (0-2 scale).
- opinion_h1n1_vacc_effective: Perceived effectiveness of the H1N1 vaccine (1-5 scale).
- opinion_h1n1_risk: Perceived risk of contracting H1N1 without vaccination (1-5 scale).
- opinion_h1n1_sick_from_vacc: Worry about sickness from H1N1 vaccine (1-5 scale).
- opinion_seas_vacc_effective: Perceived effectiveness of the seasonal flu vaccine (1-5 scale).
- opinion_seas_risk: Perceived risk of contracting seasonal flu without vaccination (1-5 scale).
- opinion_seas_sick_from_vacc: Worry about sickness from seasonal flu vaccine (1-5 scale).

Healthcare Access:
- doctor_recc_h1n1: Doctor's recommendation to get H1N1 vaccine.
- doctor_recc_seasonal: Doctor's recommendation to get seasonal flu vaccine.

Household Characteristics:
- household_adults: Number of adults in the household (capped at 3).
- household_children: Number of children in the household (capped at 3).

$$Accuracy = \frac{True\ Positives + True\ Negatives}{Total\ Instances} \quad (1)$$

$$Recall = \frac{True\ Positives}{True\ Positives + False\ Negatives} \quad (2)$$

$$Precision = \frac{True\ Positives}{True\ Positives + False\ Positives} \quad (3)$$

$$F1\ Score = 2 \times \frac{Precision \times Recall}{Precision + Recall} \quad (4)$$

Post-Explainability Techniques

The field of explainable artificial intelligence encompasses many methods that allow humans to interpret the output of artificial intelligence. In this way, people's opinions on the reasons behind and techniques used by artificial intelligence to generate prediction scores are influenced. To interpret the high-performing model's predictions both locally and globally, we applied SHAP (Shapley Additive Explanations), a well-liked explainability technique in explainable AI (Lundberg & Lee, 2017). We can understand how each feature affects predictions generally over the entire dataset (global explanation) and how particular qualities contribute to each prediction (local explanation) with the use of SHAP values.

Global Explanation

Global understanding is crucial for public health professionals and policymakers, as it highlights the most influential factors, such as medical recommendations, perceived vaccine efficacy, and underlying health conditions, in driving vaccination decisions. Such insights can guide more targeted health campaigns and interventions to improve vaccination uptake and enhance public health outcomes.

$$\hat{\phi}_j = \frac{1}{M} \sum_{m=1}^{M} \left(\hat{f}\left(x_{+j}^m\right) - \hat{f}\left(x_{-j}^m\right) \right) \quad (5)$$

In Equation 5, x is the sample of interest, j is the attribute index, f is the machine learning model, and M is the number of iterations. The prediction for x is "f^(x_(+j)^m)". However, a random number of attribute values were substituted with attribute values from a random z data points, except for the corresponding value of attribute j.To obtain all Shapley values, the process needs to be repeated for every feature.

Local Explanation

SHAP values, which illustrate the precise contribution of each feature to the vaccination likelihood for an individual respondent, provide insights into predictions at a local level. This approach is particularly valuable for case-by-case analysis, as SHAP can reveal, for example, how factors like a doctor's recommendation, perceived vaccine efficacy, or the presence of a chronic medical condition influence an individual's vaccination decision. These localized insights allow public health professionals to understand why the model assigned a specific vaccination probability to a particular respondent. Such transparency facilitates more personalized health communication strategies, enabling targeted interventions tailored to the unique concerns and circumstances of each individual.

The local SHAP value for a feature i for an instance x is given by :

where:

|S| is the number of features in subset S, f_x (S) is the model prediction using only the features in subset S,

$$\phi_j(i) = \sum_{S \subseteq N \setminus \{i\}} \frac{|S|!\,(|N| - |S| - 1)!}{|N|!} \left(f_x(S \cup \{i\}) - f_x(S) \right) \quad (6)$$

f_x (S∪{i})-f_x (S) is the marginal contribution of feature i when it is added to subset S, and N is the set of all features.

This formula generates a SHAP value that represents the feature's influence on the particular prediction by calculating the weighted average of feature I's contribution over all potential feature subsets.

Computational Tools

This study leveraged Python and its ecosystem of libraries for data analysis, model development, evaluation, and explainability. pandas and numpy were employed for efficient data manipulation and numerical computations, while matplotlib and seaborn were used for data visualization. For preprocessing, scikit-learn facilitated tasks such as label encoding, missing value imputation, and train-test splitting, and was also utilized for implementing various machine learning models. Ensemble and boosting models, including XGBoost, LightGBM, and CatBoost, were developed using their respective specialized libraries. Lastly, the SHAP library was integrated to provide both local and global explanations of model predictions, ensuring transparency and interpretability.

RESULTS

The study evaluated multiple machine learning models for predicting vaccination status. CatBoost emerged as the best-performing model, achieving an

Table 2. Evaluation results of ML models

	Models	AccuracyScore	RecallScore	PrecisionScore	F1Score
1	CatBoost	0.696	0.696	0.689	0.688
2	XGBoost	0.686	0.686	0.677	0.675
3	LGBM	0.684	0.684	0.676	0.672
4	SVM	0.683	0.683	0.674	0.669
5	Random Forest	0.680	0.680	0.672	0.672
6	KNN	0.624	0.624	0.608	0.605

accuracy of 0.696 and an F1 score of 0.688, effectively handling the dataset's complexities. Gradient boosting models, XGBoost and LightGBM, followed closely with accuracy scores of 0.686 and 0.684, respectively, showcasing strong recall and precision. SVM demonstrated competitive performance with an accuracy of 0.683, while Random Forest showed balanced results with an accuracy of 0.680 and an F1 score of 0.672. KNN, though suitable for simpler tasks, achieved lower metrics, emphasizing its limitations with high-dimensional data

SHAP Global Interpretation

SHAP (Shapley Additive Explanations) values were calculated to provide a global interpretation of the CatBoost model's predictions for the "No vaccination received" group, as visualized in the summary plot (Figure 2). This analysis highlights the influence of each feature on the model's predictions, revealing both the direction and magnitude of their impact. Features like opinion_seas_risk, opinion_seas_vacc_effective, and doctor_recc_seasonal emerged as the most influential, reflecting their strong association with vaccination behavior.

High values of opinion_seas_risk (indicating a perceived low risk of seasonal flu) and opinion_seas_vacc_effective (skepticism about vaccine effectiveness) were positively associated with the prediction of not vaccinating. Conversely, the absence of doctor recommendations (doctor_recc_seasonal and doctor_recc_h1n1) strongly increased the likelihood of no vaccination, emphasizing the critical role of healthcare providers. Demographic factors like age_group and health_worker also contributed, with younger individuals and non-healthcare workers being less likely to vaccinate. Additionally, socioeconomic factors such as income and education showed smaller yet consistent effects, with higher levels generally reducing the likelihood of no vaccination.

SHAP Local Interpretation

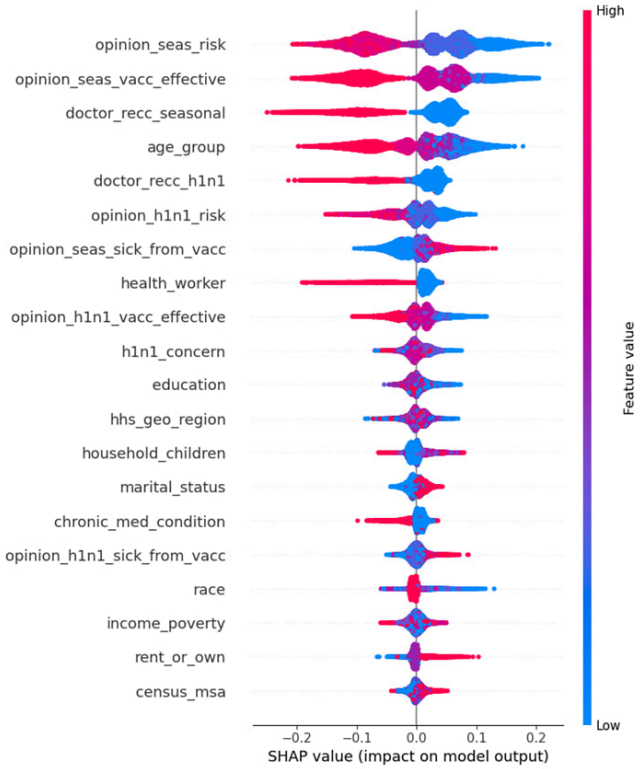

Figure 2. SHAP summary plot for global explanation of the prediction model

Two samples were selected for local interpretation: one with the target variable "Single vaccination" and the other with "No vaccination received," as these groups are critical for understanding decision patterns. The SHAP values for each sample were visualized using waterfall plots, which display the cumulative effect of each feature on the baseline prediction (mean model prediction). Features with positive contributions (red bars) increase the

likelihood of the predicted outcome, while negative contributions (blue bars) decrease it, with bar lengths reflecting the magnitude of their impact (Molnar, 2020).

For the "No vaccination received" sample (Figure 3), the baseline prediction (E[f(x)] = 0.443) was adjusted by individual features to yield a final probability of f(x) = 0.83. Key factors included opinion_seas_risk, which had the largest positive contribution (+0.13), reflecting the

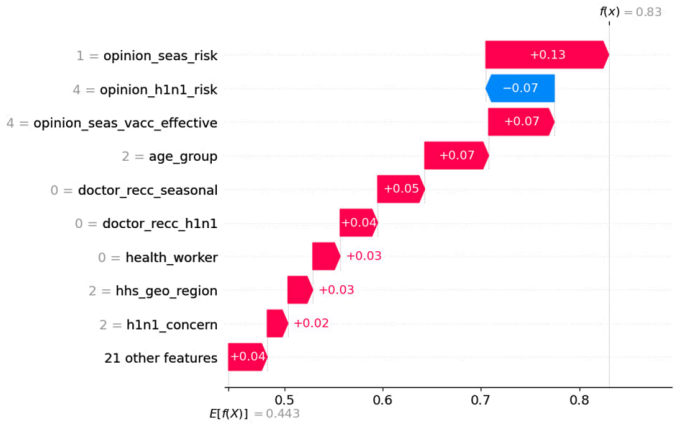

Figure 2. SHAP Waterfall plot of Sample 1 (No vaccination)

individual's perception of low seasonal flu risk, and opinion_seas_vacc_effective (+0.07), indicating skepticism about vaccine effectiveness. The absence of doctor recommendations for both seasonal and H1N1 vaccines also strongly reinforced this outcome. Other features, such as age group and non-healthcare worker status, further contributed to the prediction.

SHAP waterfall graph in Figure 4 explains the contribution of features to predicting "Single vaccination received" for a specific respondent. Starting from the baseline value (E[f(x)] = 0.349), feature contributions led to

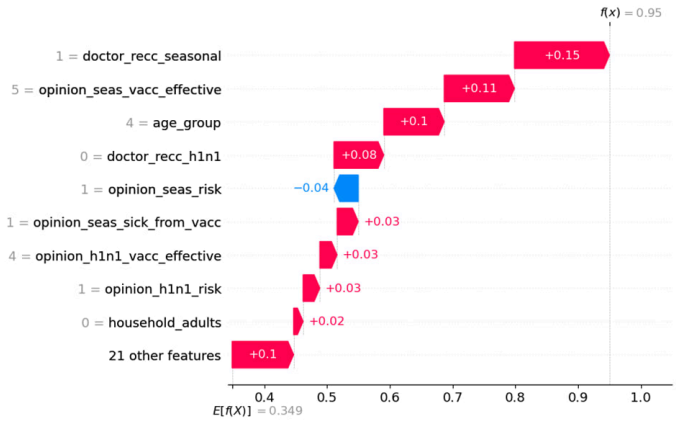

Figure 4. SHAP Waterfall plot of Sample 2 (Single vaccination)

a final probability of f(x) = 0.95. The strongest predictor was the doctor's recommendation for seasonal vaccination (+0.15), followed by a belief in the high effectiveness of the seasonal vaccine (+0.11) and the respondent's age group (+0.10), which aligns with groups more likely to vaccinate. While the absence of an H1N1 vaccine recommendation contributed positively (+0.08), the perceived low risk of seasonal flu slightly decreased the likelihood (-0.04). Other factors, such as a positive perception of vaccine effectiveness and minimal concern about vaccine side effects, added minor but consistent positive impacts.

DISCUSSION

In our study, we utilized machine learning models and explainable artificial intelligence (XAI) methods to predict and interpret behaviors related to H1N1 and seasonal flu vaccinations. These approaches provided critical insights into the factors influencing both individual and population-level vaccination decisions. The results, derived from the CatBoost model, highlighted the importance of perceptions of vaccine effectiveness, doctor recommendations, and demographic characteristics in shaping vaccination behaviors. SHAP analyses offered both global and local interpretations, contributing not only to understanding model performance but also to uncovering the underlying reasons behind vaccination decisions.

The global SHAP analysis revealed that doctor recommendations (for both seasonal and H1N1 vaccines), opinions on vaccine effectiveness, and demographic factors such as age group were the most influential features. These findings align with prior studies emphasizing the pivotal role of healthcare providers in vaccination uptake and the impact of public perceptions of vaccine efficacy (Pappaioanou & Gramer, 2010; Kim, 2021). Such insights suggest that targeted public health interventions should focus on enhancing doctor-patient communication and addressing vaccine skepticism through educational campaigns. For instance, training healthcare providers to proactively recommend vaccinations and effectively communicate their benefits could directly improve vaccination rates.

The local interpretation of a sample classified as "No vaccination received" highlighted specific barriers to vaccination, including a low perceived risk of seasonal flu, skepticism about vaccine effectiveness, and the absence of doctor recommendations. These results are consistent with findings from Ebulue et al. (2024), which noted that perceived risks alone are insufficient to motivate

preventive actions. Addressing these barriers may involve tailored educational initiatives that counteract misinformation about vaccine efficacy and targeted outreach efforts in communities with low vaccination uptake.

In contrast, the local interpretation for a "Single vaccination received" case underscored the critical role of positive interactions with healthcare providers and trust in vaccine effectiveness. The individual's decision was strongly influenced by the recommendation of a seasonal vaccine and a belief in its efficacy. These insights suggest strategies such as implementing reminder systems for individuals who receive one vaccine to encourage follow-up vaccinations, and emphasizing the complementary benefits of both seasonal and H1N1 vaccinations in public health messaging.

CONCLUSION

In conclusion, the integration of global and local insights through SHAP provides actionable strategies to improve vaccination rates. Globally, the findings support the prioritization of doctor recommendations and efforts to combat vaccine skepticism. Locally, personalized interventions, such as reminders and tailored messages, can address individual concerns. Together, these approaches offer a robust framework for enhancing public health strategies and preparing for future pandemics.

ETHICAL APPROVAL

The dataset used in this study is anonymized and publicly accessible, ensuring compliance with ethical standards for secondary data analysis. Since the data does not include identifiable personal information, ethical approval was not required for its use.

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AUTHOR CONTRIBUTIONS

Conceptualization, B.C., methodology, B.C and A.Y.; software, A.Y; validation, B.C and A.Y.; formal analysis, B.C..; investigation, B.C and A.Y.; resources, B.C.; data curation, B.C.; writing—original draft preparation, B.C and A.Y.; writing—review and editing, TBD.; visualization, A.Y.; supervision, B.C. All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTEREST

The authors declared that there is no conflict of interest.

RESEARCH FUNDING

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DATA AVAILABILITY

The data utilized in this study was acquired from an open-source report: Centers for Disease Control and Prevention, 2012. “2009 H1N1 Pandemic (H1N1pdm09 virus),”, accessed 14 October 2024. Available at https://www.cdc.gov/flu/pandemic-resources/2009-h1n1-pandemic.html. An alternative version of this dataset is also accessible via Kaggle: https://www.kaggle.com/datasets/arashnic/flu-data .

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Review Article

The Effects of Leptin and Ghrelin Hormones on Metabolism

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ABSTRACT

Leptin was first identified in 1994 by Zhang and colleagues as a signaling factor originating from adipose tissue. Its name is derived from the Greek word “leptos,” meaning “thin” or “slender”. While its primary site of secretion is white adipose tissue, leptin is also secreted in smaller amounts by brown adipose tissue, as well as by the placenta, skeletal muscle, stomach, mammary epithelium, and brain tissue. By acting at the hypothalamic level, leptin reduces appetite. Leptin is a 16-kilodalton, single-chain polypeptide hormone. Initially recognized for its role in satiety and energy balance, leptin was later identified as an anti-obesity factor that exerts feedback effects from adipocytes to the hypothalamus. It has been reported as a key physiological factor in mammals for preventing fat accumulation.Ghrelin, discovered in 1999 by Kojima and colleagues in the stomachs of mice, is a 28-amino acid oligopeptide hormone that stimulates the release of growth hormone. Although primarily secreted by stomach tissue, ghrelin is also produced by the brain, intestines, placenta, kidneys, pituitary gland, and pancreas. The name “ghrelin” is derived from the root “ghre,” meaning “grow,” in Indo-European languages, combined with “relin,” which implies secretion. Ghrelin is also referred to as the "appetite hormone. Isolated from mouse stomach tissue, this 28-amino acid peptide plays crucial physiological roles. Ghrelin has been reported to increase food intake, promote positive energy balance, and influence gastrointestinal motility, cell proliferation, bone metabolism, and reproduction.

Key words: Leptin, Ghrelin, Hormone, Metabolism

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INTRODUCTION

General Structure of Leptin and Ghrelin

Leptin is a peptide hormone with a molecular weight of 16 kDa, primarily recognized for its role in regulating body weight (Williams et al., 2002). Its structure resembles that of cytokines. In recent years, extensive research has been conducted on the synthesis, secretion, receptors, and effects of leptin. These studies have demonstrated that leptin influences appetite, hunger, energy expenditure, and reproduction (Wolinski et al., 2014).

The primary role of leptin in the body is to regulate food intake and energy metabolism via negative feedback to the brain, thereby preventing obesity. Moreover, leptin plays critical roles in regulating metabolism, reproduction, puberty, immunity, gastrointestinal functions, sympathetic nervous system activation, angiogenesis, and osteogenesis. Initially identified for its involvement in satiety and energy balance, leptin was later found to act as an anti-obesity factor with feedback effects from adipocytes to the hypothalamus (Zhang et al., 1994).

Leptin production and plasma levels in animals can vary depending on genetic factors such as species and breed, physiological factors like age, pregnancy, lactation, and feeding habits, as well as environmental conditions such as temperature and light (Williams et al., 2002).

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Ghrelin, primarily produced by X(A) cells in the fundus of the stomach with endocrine functions, is a 28-amino-acid lipopeptide hormone and the endogenous ligand of the growth hormone secretagogue receptor (Kojima et al., 1999). It is synthesized in the stomachs of humans and rodents, as well as in the abomasum and rumen tissues of cattle, playing a role in regulating food intake and energy balance in ruminants (Hayashida et al., 2001; Biçici and Karakurum; 2024).

Beyond the stomach, ghrelin is also synthesized in the hypothalamus, pituitary gland, salivary glands, thyroid, small intestine, kidneys, heart, alpha, beta, and epsilon cells of the pancreas, central nervous system, lungs, placenta, gonads, immune system, and mammary glands (Kojima et al., 1999).

Ghrelin's most significant effect is its strong stimulation of growth hormone secretion from somatotropic cells in the pituitary gland. In addition to this activity, ghrelin exhibits orexigenic effects, stimulates acid secretion, regulates gastric motility and pancreatic activity, affects sleep, contributes to cardiovascular functions, and exerts antiproliferative effects on various cells (Casanueva et al., 2004).

Ghrelin mRNA has been detected in nearly all tissues, with the highest levels observed in the fundus of the stomach. This is followed by the jejunum, duodenum, antrum of the stomach, lungs, pancreas, venous system, gallbladder, lymph nodes, esophagus, left colon, buccal mucosa, pituitary gland, mammary gland, kidneys, ovaries, prostate, right colon, ileum, liver, spleen, fallopian tubes, lymphocytes, testes, adipose tissue, placenta, adrenal glands, muscles, bladder, atrium of the heart, thyroid gland, myocardium, and skin (Hayashida et al., 2001).

Ghrelin has been reported to increase food consumption and promote a positive energy balance. Additionally, it influences gastrointestinal motility, cell proliferation, bone metabolism, and reproductive activities (Zizzari et al., 2011).

Relationship Between Leptin and Ghrelin

Leptin, secreted by adipose tissue, and ghrelin, secreted by the stomach, are significant hormones discovered in recent years that play critical roles in energy balance regulation.

Leptin and ghrelin operate within the organism based on the "Yin-Yang" principle. In other words, the concentrations of ghrelin and leptin are controlled via a feedback mechanism involving Y neurons in the hypothalamus, which helps regulate body weight. The levels of these hormones are influenced by factors such as hunger-satiety, glucose levels, diet, insulin, gut hormones, parasympathetic activity, age, pregnancy, obesity, gender, polycystic ovary syndrome, energy levels, insulin resistance, diabetes mellitus, GH deficiency, acromegaly, hypo- and hyperthyroidism, the neonatal period, and certain neuroendocrine gastrointestinal tumors. Intracerebroventricular administration of leptin has been observed to increase arterial pressure, whereas administration of ghrelin reduces it (Nagaya et al., 2001).

Recent studies suggest that leptin, in conjunction with ghrelin, a hormone produced by the gastrointestinal system, regulates energy metabolism by influencing specific neurons in the central nervous system. Unlike leptin, ghrelin is reported to have appetite- and fat-increasing properties (Yiş et al., 2005).

Effects of Leptin and Ghrelin on Metabolism

Effects on Food Intake

Feeding is a fundamental behavior necessary for survival. Appetite regulation is considered to be under the control of the brain, particularly through the complex mechanisms of the central nervous system and the hypothalamus. Removal of the lateral hypothalamus results in hypophagia, leading to severe weight loss and eventual death. Conversely, removal of the ventromedial hypothalamus causes hyperphagia, leading to increased feeding frequency and food intake, resulting in significant weight gain and severe obesity. Thus, feeding behavior is regulated by a balance of stimulatory and inhibitory forces in the hypothalamus (Kojima et al., 1999).

One of ghrelin's earliest discovered effects is its relationship with growth hormone (GH). Intravenous administration of ghrelin in humans and dogs stimulates GH release. Ghrelin increases GH secretion in a dose-dependent manner in both in vitro and in vivo conditions (Date et al., 2000).

Ghrelin's appetite-stimulating effect is as potent as neuropeptide Y (NPY), which is known to be the strongest appetite stimulator. Ghrelin promotes feeding behavior by activating NPY/AgRP neurons in the hypothalamus. NPY (neuropeptide Y) and agouti-related protein (AgRP) are produced by the same neuronal population in the arcuate nucleus (ARC). Their appetite-stimulating effects are directly inhibited by leptin. Leptin suppresses ghrelin-induced food intake, whereas ghrelin reverses leptin's appetite-suppressing effect. This indicates that ghrelin antagonizes leptin's role in the regulation of the NPY/AgRP system (Hosoda et al., 2002).

Leptin prevents excessive weight gain by inhibiting anabolic signaling pathways that promote weight gain in the brain and activating catabolic signaling pathways that increase energy expenditure. In addition to leptin, the gastrointestinal system sends signals to the brain to regulate meal size and frequency. Some of these signals are mechanical impulses resulting from gastrointestinal tract distension, while the majority are transmitted via the afferent branches of the vagus nerve. The first and most critical hormonal satiety signal transmitted through the vagus nerve is cholecystokinin (CCK). Leptin also works in synergy with CCK and enhances sensitivity to it, reducing meal size (Daniel et al., 2002).

Effects on Energy Metabolism

In recent years, it has been suggested that leptin, along with the ghrelin hormone produced by the gastrointestinal system, plays a role in regulating energy metabolism by influencing specific neurons in the central nervous system. Unlike leptin, ghrelin is reported to have appetite- and fat-increasing properties (Yiş et al., 2005).

Leptin concentration correlates with the amount of energy stored in fat and the body's energy balance. Plasma leptin levels are higher in obese individuals compared to lean ones, drop rapidly during fasting, and rise again after feeding (Ahima et al., 2000).

Leptin has a short-term stimulatory effect on lipid oxidation in skeletal muscles. It reduces lipid stores in skeletal muscles by increasing fatty acid catabolism. Intravenous leptin administration decreases triacylglycerol secretion in the liver while enhancing fatty acid oxidation. In the liver, it reduces triglyceride content and boosts fatty acid oxidation. Additionally, by activating the sympathetic nervous system and increasing thyroid hormones, leptin enhances thermogenesis and acts as a regulator of energy metabolism (Suzuki et al., 2007).

Ghrelin plays roles in growth hormone release, energy balance, food intake, and body weight regulation. It is described as a hormone that prevents energy depletion and cachexia. Its serum levels rise before each meal, stimulating appetite (Soriana et al., 2004). Studies in mice have shown that fasting increases ghrelin secretion, while carbohydrate intake suppresses it (Cummings ve ark 2001). Ghrelin's effects on energy homeostasis occur primarily in the hypothalamus of the central nervous system, indicating that its impact extends beyond the peripheral tissues where it is produced (Rindi et al., 2002).

Over the past 15 years, significant progress has been made in understanding the effects of leptin and ghrelin on energy balance, neuroendocrine function, and various physiological processes. Insights into the biology of leptin and ghrelin under normal and pathological conditions can aid in the diagnosis and treatment of obesity and related metabolic diseases (Ahima et al., 2000).

Effects on the Cardiovascular System

Ghrelin mRNA has been detected in the heart and aorta. Intracerebroventricular (ICV) injection of ghrelin into the nucleus tractus solitarius in rats suppresses sympathetic activity, leading to reductions in blood pressure and heart rate, a mechanism opposite to that observed with leptin (Zhang et al., 1994). Additionally, ghrelin administration in rats increases left ventricular stroke volume. In hypophysectomized rats, ghrelin administration has been associated with healthy heart development. Ghrelin also counteracts the vasoconstrictive effects of endothelin-1 in arteries, indicating a role in vascular homeostasis (Morton et al., 2001).

Effects on the Immune System

Leptin plays a regulatory role in immune system functions (Barb et al., 2001). It stimulates leukocyte synthesis and enhances the erythropoietic effects of erythropoietin on red blood cells. Like bacterial antigens, leptin activates macrophages, increases their phagocytic activity, and stimulates the secretion of both pro-inflammatory and anti-inflammatory cytokines from macrophages (Hekimoğlu, 2006).

Recent studies have uncovered the functional roles of ghrelin and other growth hormone secretagogues within the immune system, especially under conditions of inflammatory stress and injury. Over the past decade, numerous reports have described ghrelin as a potent anti-inflammatory agent, showing promise as a therapeutic substance for treating inflammatory diseases and injuries in both in vivo and in vitro settings. Additionally, ghrelin has been shown to support lymphocyte development in primary lymphoid organs (bone marrow and thymus) and reverse age-related thymic involution (Patel et al., 2011).

DISCUSSION

The interplay between leptin and ghrelin highlights a complex regulatory mechanism governing energy metabolism and physiological functions. While leptin primarily acts as a satiety signal to reduce food intake and prevent excessive fat accumulation, ghrelin functions as an appetite stimulant, promoting energy storage and

positive energy balance. This "Yin-Yang" dynamic suggests a finely tuned feedback system within the hypothalamus to maintain energy homeostasis. Leptin's role extends beyond metabolism, influencing immune responses and cardiovascular regulation by activating sympathetic pathways and modulating cytokine release. Conversely, ghrelin not only stimulates growth hormone secretion but also exhibits anti-inflammatory properties and supports cardiovascular and immune health. These findings underscore the therapeutic potential of targeting leptin and ghrelin pathways for managing obesity, metabolic disorders, and inflammatory diseases. Further research into these hormones' interactions may offer insights into novel treatment strategies for metabolic and systemic disorders.

CONFLICT OF INTEREST

There is no conflict of interest.

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