

UDC: 616-021.5:616.12-008.314

DOI: 10.24061/2413-4260.XVI.1.59.2026.28

SPECIFIC FEATURES OF ALLERGIC REACTIONS
IN PATIENTS WITH COMORBIDITIES:
BRADYKININ-MEDIATED REACTIONS

*N. Kaspruk, S. Batranovska,
S. Melnychuk, T. Kopchuk,
T. Unhuryan, A. Petriuk*

Bukovinian State Medical University
(Chernivtsi, Ukraine)

Summary.

Allergic disorders constitute a significant problem that substantially impairs quality of life, engages practitioners across multiple medical specialties, and imposes a considerable economic burden on healthcare systems. Unsatisfactory therapeutic outcomes in comorbid conditions are frequently attributable to pharmacological hypersensitivity. The widespread and increasing use of angiotensin-converting enzyme (ACE) inhibitors has been associated with a marked rise in the incidence of angioedema. Accurate differentiation among the various forms of angioedema therefore remains a critical element of the diagnostic process.

The aim of the work was to analyse the features of hypersensitivity reactions in patients with diabetes mellitus, to examine the characteristics of angioedema cases, and to improve the diagnosis, prognosis, and prevention of this pathology.

The attention of practitioners in therapeutic and surgical specialties should be directed towards the specific features of angioedema in patients receiving angiotensin-converting enzyme inhibitor therapy.

Materials and methods. Outpatient medical records and case histories of 188 patients with diabetes mellitus who had documented episodes of reactions classified as allergic (main group) and of 122 patients with similar reactions but without diabetes mellitus over a 10-year period (2015-2024) were analysed. Within the main group, a subgroup of 48 patients with hypersensitivity reactions manifesting as angioedema and/or acute urticaria was identified. Data from questionnaires completed by patients who consulted the Department of Clinical Immunology, Allergology and Endocrinology during the specified period were also analysed. General clinical, biochemical, immunoenzymatic, instrumental, statistical, and analytical methods were employed. The study was conducted in accordance with the fundamental principles of bioethics as set out in the World Medical Association Declaration of Helsinki. Clinical data were analysed retrospectively on the basis of medical documentation and questionnaires. Informed consent for the use of the obtained data in scientific research was provided by patients who completed questionnaires and underwent consultative examination. All personal data were anonymised and used exclusively for scientific purposes. No additional invasive interventions were performed, and no risk to patient health was incurred. Statistical processing was performed using descriptive and comparative statistical methods. Data are presented as absolute and relative values (%). Comparisons between groups were conducted with account taken of clinical and anamnestic characteristics. Correlation analysis was applied to assess the relationship between the duration of diabetes mellitus and the frequency of hypersensitivity reactions. Results were considered statistically significant at $p < 0.05$. The study was performed as part of a pilot project. Further research is planned to expand the sample size and verify the obtained results.

Results and discussion. The duration of diabetes mellitus in the patients included in the study ranged from 1 to 30 years. Insulin-dependent diabetes mellitus was diagnosed in 82% of the patients. A positive history of hypersensitivity reactions to medications and food products was elicited nearly three times more frequently in patients with insulin-dependent diabetes mellitus than in the control group, and this frequency correlated directly with the duration of the disease. In recent years (2017-2024), changes were also observed in the overall structure of hyperergic reactions compared with the previously analysed period (2014-2016). A shift towards an increased proportion of cases associated with hypersensitivity reactions to medications was identified. Allergic reactions in patients with diabetes mellitus were more frequently associated with insulin preparations, antibiotics, local anaesthetics, radiocontrast agents, and cardiac medications. Among the medications to which hypersensitivity was documented or reported in the medical history, the frequency distribution was as follows: insulin preparations – 22.7%; medications affecting the digestive system and metabolic processes – 23.17%; antibiotics – 20.5%; nonsteroidal anti-inflammatory medications – 9.7%; cardiac medications – 9.1%; vitamins – 3.6%; phytoforms – up to 2%. In-depth examination of patients with episodes of angioedema included analysis of cases associated with lisinopril use in a 55-year-old woman and a 70-year-old woman who presented with abdominal pain (in the latter case accompanied by vomiting and diarrhoea). Computed tomography demonstrated oedema of the small-intestine wall. After discontinuation of the medication, no further episodes of oedema occurred during the following year. Asymmetric facial angioedema was documented in two men aged 62 and 68 years during ramipril therapy (with an uncomplicated allergic history), as well as in men aged 59 and 75 years with pronounced generalised skin itching without rashes but with isolated asymmetric oedema of the extremities during enalapril therapy. Complete discontinuation of ACE inhibitors resulted in regression of symptoms within 1 week to 2 months. In 4 of the 6 described cases, additional photosensitivity and skin hyperaesthesia were observed. Differential diagnosis primarily excluded IgE-mediated anaphylaxis but also considered hormonal disorders in women (symmetrical facial and extremity swelling), heart failure (pastiness), superior vena cava syndrome (chronic facial oedema), acute allergic contact dermatitis, erysipelas or subcutaneous inflammatory processes of the face, lymphoedema, shingles, Crohn's disease, systemic connective-tissue diseases, and acute abdomen.

Conclusions. 1. Patients with insulin-dependent diabetes mellitus exhibit a 2.9-fold higher incidence of hypersensitivity reactions compared with other therapeutic patients, with frequency directly correlating with disease duration and severity. 2. Differentiation between histamine-mediated and bradykinin-mediated angioedema constitutes a critical aspect of clinical practice. A markedly increased risk of angioedema during ACE inhibitor therapy has been demonstrated in patients with

a positive allergic history. Failure of angioedema to respond to antihistamines and corticosteroids should raise suspicion of a bradykinin-mediated aetiology. 3. Immediate discontinuation of ACE inhibitor therapy is required, with subsequent replacement by an antihypertensive agent from a different pharmacological class. 4. Knowledge of rare causes of acute abdominal pain expands the differential diagnostic spectrum for surgeons, thereby enabling avoidance of unnecessary interventions. C1-esterase inhibitor deficiency should be excluded in cases presenting with isolated angioedema of the small intestine. 5. Anaesthesiologists must be informed of potential adverse intraoperative reactions in patients on long-term treatment with certain antihypertensive medications. 6. Mandatory professional nutritional education, prevention of polypharmacy, and meticulous recording of documented hypersensitivity reactions in patient records at all levels of care are recommended as integral components of the preventive measures programme.

Keywords: ACE Inhibitors; Diabetes Mellitus; Side Effects; Angioedema; Bradykinin.

Introduction

Allergic disorders constitute a significant problem that substantially impairs quality of life in most cases, engages practitioners across multiple medical specialties, and imposes considerable costs on healthcare systems. The combination of allergic pathology and endocrinopathies is becoming increasingly relevant owing to the rising prevalence of endocrinopathies (for example, the global prevalence of diabetes mellitus has increased by more than 63% over the past 10 years, according to the International Diabetes Federation) and the rising prevalence of allergic reactions in the general population (more than 30% of the world's population has experienced at least one episode of a reaction classified as allergic). Pharmacological hypersensitivity frequently leads to unsatisfactory therapeutic outcomes in comorbid conditions. Hypersensitivity to pharmaceutical agents accounts for up to 15% of all adverse drug reactions and is reported in up to 10% of the global population [1, 2].

The vast majority of epidemiological studies on allergic diseases have been performed either as population surveys or through analysis of medical statistics derived from healthcare institution records of patient visits. These approaches significantly complicate the interpretation of results, since the choice of research method substantially influences the findings [2, 3].

Primary care and emergency physicians are usually the first to encounter patients with angioedema (AE). Cases of suspected non-allergic AE are uncommon at this level of care, and referral to a specialist is infrequent [4, 5]. Even experienced allergists may not always recognize bradykinin-mediated angioedema. The increasing use of angiotensin-converting enzyme (ACE) inhibitors has been associated with a rise in the incidence of AE. Statistically, 0.1-0.5% of patients experience episodes of AE, which may occur in the first month or even several years after initiation of therapy. The actual incidence is likely higher, as not all adverse reactions are reported through pharmacovigilance systems. [6, 7, 8].

Differentiation among the various forms of AE is a critical component of diagnosis. The mechanism underlying the AE variant under discussion involves accumulation of bradykinin (BK) secondary to ACE inhibitors; C1-esterase inhibitor (C1-INH) is also a potent regulator of the bradykinin system. Other medications, such as immunosuppressants, certain antidiabetic agents, or calcium antagonists, may increase the likelihood of ACE inhibitor-associated angioedema when used concurrently.

Bradykinin-mediated AE typically responds poorly to antihistamines, is dose-independent, and can be potentially life-threatening [9, 10, 11].

The incidence of angioedema induced by ACE inhibitors has increased significantly in recent years. This class of medications is currently used by approximately 40 million people worldwide. With the growing prescription of ACE inhibitors, including during periods of martial law, the problem is becoming increasingly urgent. Thousands of patients with various conditions (hypertension, diabetes mellitus, heart failure, chronic kidney disease) are prescribed ACE inhibitors daily, making an increase in the incidence of drug-induced angioedema predictable. For example, in the United States, more than 100,000 annual emergency department visits are registered for ACE inhibitor-induced angioedema, accounting for up to 50% of all angioedema cases detected in emergency departments [12, 13].

Since patients do not respond to anti-H1 antihistamines and corticosteroids, early clinical recognition and discontinuation of ACE inhibitors are the treatments of choice for long-term management of ACE inhibitor-induced angioedema. Given that histamine-mediated allergic angioedema and bradykinin-mediated nonallergic angioedema require different therapeutic approaches, differentiation between them is essential [12, 14].

The swelling usually lasts from a few hours to 72 hours and manifests as non-pruritic subcutaneous or submucosal oedema. It is characterised by localised swelling resulting from histamine release. Itching is rare, and the most commonly affected areas are the hands, feet, face, and genitalia, with periorbital swelling being the most frequent presentation [15]. The most common clinical presentations of AE are oropharyngeal and periorbital oedema. Isolated small-intestinal angioedema is considered rare and often remains undiagnosed because its clinical and radiological manifestations resemble those of small-intestinal ischaemia, enteritis, lymphoma, vasculitis, C1-INH deficiency, and Crohn's disease.

The mechanism of bradykinin formation in IgE-mediated reactions is multifactorial. It involves not only tissue secretion of kallikrein but also direct activation of the plasma cascade by secreted heparin, activation on the surface of endothelial cells, and the influence of connective-tissue proteoglycans.

Bradykinin is generated through the interaction of factor XII, prekallikrein, and high-molecular-weight kininogen on negatively charged inorganic

surfaces and macromolecular organic surfaces or through assembly along the cell surface. Catalysis along the cell surface requires zinc-dependent binding of factor XII and high-molecular-weight kininogen to proteins such as the receptor for the globular head of the complement subcomponent C1q, cytokeratin 1, and the urokinase plasminogen activator receptor. These three proteins form a complex within the cell membrane, and initiation depends on autoactivation of factor XII upon binding to gC1qR (receptor for the globular heads of the subcomponent of complement C1q). A factor XII-independent bypass mechanism also exists that requires a cellular cofactor or protease capable of activating prekallikrein. Bradykinin is degraded by carboxypeptidase N and angiotensin-converting enzyme. Bradykinin-mediated angioedema results from hereditary or acquired C1-INH deficiencies or from the use of ACE inhibitors in the treatment of hypertension, heart failure, diabetes mellitus, or scleroderma. Bradykinin contributes to tissue hyperresponsiveness, local inflammation, and hypotension in allergic rhinitis, asthma, and anaphylaxis. Activation of the plasma cascade occurs as a result of heparin release and endothelial cell activation and as a secondary event in other inflammatory pathways. Any local dilution of plasma components reduces the effect of protease inhibitors and increases the rate of enzymatic reactions leading to enhanced kinin formation [1].

Recent data indicate that the mechanisms underlying angioedema are heterogeneous and complex. Examples include disinhibition of the kallikrein-kinin system, leading to local and transient excess production of bradykinin (as in hereditary or acquired C1-INH deficiency), reduced catabolism of bradykinin (drug-induced), and intrinsic abnormalities in elements of the vascular endothelium [16, 18].

In contrast to C1-INH deficiency (hereditary angioedema – HAE), the role of bradykinin in ACE inhibitor-induced angioedema is less clearly defined but is considered important, whereas its role in the pathogenesis of anaphylaxis remains poorly understood. Evidence indicates that the plasma bradykinin-forming cascade is activated in IgE-mediated anaphylaxis, with heparin released from mast cells acting as the initiator. This mechanism is observed in allergic rhinitis, allergic asthma, chronic spontaneous urticaria, and anaphylaxis. These reactions are frequently accompanied by systemic and local elevations in bradykinin levels. Because the effects of bradykinin are not blocked by adrenaline, severe anaphylaxis, particularly shock, often responds poorly to its administration. This phenomenon is described in the literature as refractory anaphylaxis. Many agents approved for the treatment of HAE due to C1-INH deficiency may be effective. For example, icatibant can be used to block bradykinin, and lanadelumab can be administered to prevent further bradykinin production. Both agents can be given intravenously or subcutaneously. Since ACE inhibitor-induced angioedema results from inhibition of bradykinin breakdown (or possibly other peptides inactivated by ACE) rather than excessive production,

icatibant is the only agent among those used for hereditary angioedema that has demonstrated efficacy [9].

The aim of the work was to analyse the features of hypersensitivity reactions in patients with diabetes mellitus, to examine the characteristics of AE cases, and to improve diagnosis, prognosis, and prevention of this pathology.

The attention of medical practitioners in therapeutic and surgical specialties should be directed towards the specific features of AE in patients receiving ACE inhibitor therapy.

Materials and methods

Outpatient medical records and case histories of 188 patients with diabetes mellitus who had documented episodes of reactions classified as allergic (main group) and of 122 patients with similar reactions but without diabetes mellitus over a 10-year period (2015-2024) were analysed. Within the main group, a subgroup of 48 patients with hypersensitivity reactions manifesting as AE and/or acute urticaria was identified.

The following methods were employed: general clinical, biochemical, immunoenzymatic, instrumental, statistical, and analytical.

Data from questionnaires completed by patients who consulted the Department of Clinical Immunology, Allergology and Endocrinology during the specified period were also analysed (Figure 1).

To verify the diagnosis, the following diagnostic algorithms were used (Figure 2).

A systematic literature search of PubMed covering the past 12 years was performed using the MeSH term «angioedema» (65 results) in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [19, 20, 21]. All studies were published in English.

The study was conducted in accordance with the fundamental principles of bioethics as set out in the World Medical Association Declaration of Helsinki. Clinical data were analysed retrospectively on the basis of medical documentation and questionnaires. Patients who completed the questionnaire and underwent consultative examination provided informed consent for the use of their data in scientific research. All personal data were anonymised and used exclusively for scientific purposes. The study did not involve additional invasive interventions and posed no risk to patient health.

Statistical processing was performed using descriptive and comparative statistical methods. Data are presented as absolute and relative values (%). Comparisons between groups were conducted with account taken of clinical and anamnestic characteristics. Correlation analysis was applied to assess the relationship between the duration of diabetes mellitus and the frequency of hypersensitivity reactions. Results were considered statistically significant at $p < 0.05$.

The study was performed as part of a pilot project. Further research is planned to expand the sample size and verify the obtained results.

| | |
|---|---|
| Patient name (MRN): | Date of Interview: |
| Has the patient ever experienced a reaction to vaccine or during surgery? | |
| Does the patient have any chronic diseases? | |
| Is there family history of adverse reactions? | |
| 1. Suspected medication(s) (route, dose, etc). OTHER medications taken at the time of the reaction. | |
| 2. Cutaneous symptoms (location, duration, appearance, pruritic?) | Non cutaneous symptoms (e.g., headache, GI symptoms, etc) |
| 3. When did the reaction occur? Did the reaction occur at CMH? | |
| 4. Number of doses received before the onset of the reaction. | |
| 5. Have similar symptoms occurred while not taking the medication? (yes/no) | |
| 6. Have similar symptoms occurred while taking any other medications? (yes/no) | |
| 7. Are there other medications in the same class that the patient can tolerate? | |
| 8. Concurrent illness at the time of the reaction | |
| 9. Previous treatment with the suspected medication? When? | |
| 10 Treatment administered for the reaction? | |

Figure 1. Adverse Medication Reaction Questionnaire.

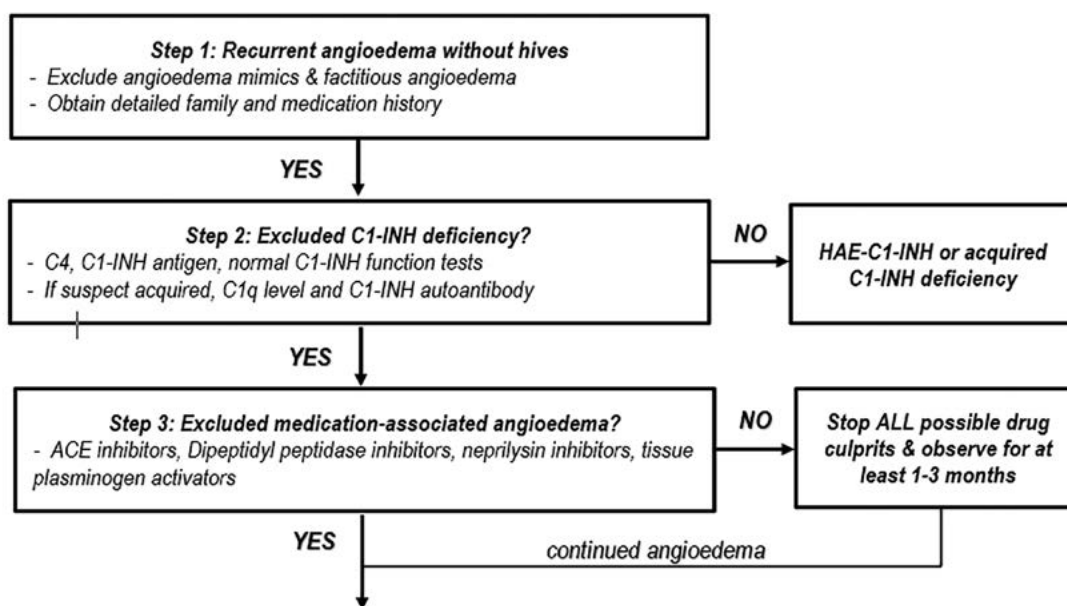


Figure 2. Fragment of diagnostic algorithms used to verify the diagnosis.

Results and discussion

The duration of diabetes mellitus in the patients included in the study ranged from 1 to 30 years. Insulin-dependent diabetes mellitus was diagnosed in 82% of the patients.

A positive history of hypersensitivity reactions to drugs and food products was elicited nearly three times more frequently in patients with insulin-dependent diabetes mellitus than in the control group, and this frequency correlated directly with the duration of the disease. In recent years (2017-2024), changes were also observed in the overall structure of hypersensitivity reactions compared with the previously analysed period (2014-2016). A shift towards an increased proportion of cases associated with drug hypersensitivity reactions was identified. Allergic reactions in patients with diabetes mellitus were more frequently associated with the administration of insulin preparations, antibiotics, local anaesthetics, radiocontrast agents, and cardiac medications.

Among the medications to which hypersensitivity was documented or reported in the medical history, the frequency distribution was as follows: insulin preparations – 22.7%; medications affecting the digestive system and metabolic processes – 23.17%; antibiotics – 20.5%; nonsteroidal anti-

inflammatory drugs – 9.7%; cardiac medications – 9.1%; vitamins – 3.6%; phytoforms – up to 2%.

Among the agents used to manage complications of diabetes mellitus, cardiovascular medications, particularly ACE inhibitors, occupy a pre-eminent position. Experimental and epidemiological data indicate that activation of the renin-angiotensin-aldosterone system plays an important role in the development of micro- and macrovascular complications in patients with diabetes mellitus. For the same degree of blood pressure control, ACE inhibitors provide functional and tissue protection of target organs compared with other antihypertensive agents. These effects result from inhibition of both the haemodynamic and tissue actions of angiotensin II. Furthermore, a growing body of evidence favours the use of ACE inhibitors at a very early stage in patients with diabetes mellitus [22].

The potential risk of bradykinin-mediated oedema in pregnant women with hypertension is also of particular concern. This risk is attributed to physiological changes during pregnancy, namely increased production of vasoactive peptides, particularly bradykinin, which is associated with activation of the renin-angiotensin-aldosterone system and

an increased requirement for vasodilation to ensure placental blood flow [23]. No published data on the incidence of urticaria and angioedema during pregnancy are available; however, since the condition occurs in young women, the incidence is probably the same as or even higher than in the general population. According to international guidelines on the gynaecological and obstetric management of female patients with HAE, a higher attack rate has been reported in the first trimester of pregnancy. Some reports also indicate an increase in attack rates in the second or third trimester. The rapid elevation in oestrogen levels at the beginning and end of pregnancy together with the increase in prolactogenic hormones is considered responsible for this rise, whereas the balance between oestrogen and progesterone in the second trimester reduces the attack rate. Cessation of chronic medications such as danazol during pregnancy is mandatory because of its virilising effect on the fetus, but it often leads to exacerbations. During pregnancy, attacks occur more frequently in the abdomen, sometimes mimicking uterine contractions and surgical emergencies. In several case reports, a higher attack rate was also observed during the puerperium [24, 25].

Following in-depth examination of patients with episodes of AE, the cases were analysed, in particular, those associated with lisinopril use in a 55-year-old woman and a 70-year-old woman who presented with abdominal pain (in the latter case accompanied by vomiting and diarrhoea). Computed tomography demonstrated oedema of the small-intestine wall. After discontinuation of the medication, no further episodes of oedema occurred within 1 year. Episodes of asymmetric facial AE were observed in two men aged 62 and 68 years during ramipril therapy (with no relevant allergic history), as well as in men aged 59 and 75 years with pronounced generalised pruritus without rash but with isolated asymmetric oedema of the extremities during enalapril therapy. After complete discontinuation of ACE inhibitors, regression of symptoms occurred within 1 week to 2 months. In 4 of the 6 described cases, additional photosensitivity and cutaneous hyperaesthesia were observed.

Differential diagnosis primarily excluded histaminergic and hereditary variants of AE, as well as hormonal disorders in women, heart failure, superior vena cava syndrome, inflammatory processes in the subcutaneous tissue of the face, lymphoedema, herpes zoster, Crohn's disease, systemic connective tissue diseases, and acute abdomen.

Differentiation of acquired AE variants was based on the classification of all variants into the following groups:

- Idiopathic histaminergic AE: responds to treatment with antihistamine drugs; represents the most common form of AE. Histamine released from cutaneous mast cells following exposure to an allergen (food, drugs, insect venom) is likely involved in the pathogenesis, although the responsible factor is not always identifiable.

- Idiopathic non-histaminergic AE: does not respond to treatment with antihistamines; bradykinin likely plays the main role in pathogenesis.

- AE associated with the use of ACE inhibitors: occurs due to an increase in the concentration of bradykinin, which is normally inactivated by ACE. Additionally, ACE neutralises a number of neurokinins, particularly substance P and neurokinin A, which are important in the pathogenesis of AE. It remains unclear why some patients also develop

oedema after taking an angiotensin receptor blocker (0.13% of patients taking these drugs), although it is generally known that these drugs do not affect kinin metabolism.

- AE associated with C1-INH deficiency: the pathomechanisms of this type are diverse; the cause may be neutralising antibodies against C1-INH.

Currently, no specific laboratory biomarkers exist to confirm the diagnosis of AE caused by ACE inhibitors. Key biomarkers that may assist in confirming the diagnosis of ACE inhibitor-induced angioedema include the following:

1. Elevated plasma bradykinin serve as a key indicator.

2. Plasma kallikrein activity is increased due to stimulation of the kinin–kallikrein system (an important enzyme involved in the release of bradykinin).

3. C1 inhibitor levels (normal values likely exclude hereditary or acquired AE syndrome associated with C1-INH deficiency).

4. Moderate increase in D-dimers (in severe AE, the blood coagulation system may be activated, resulting in the formation of microthrombi and their subsequent lysis, which explains the increase in D-dimers).

5. Increased nitric oxide (NO) levels. bradykinin stimulates the production of NO through the activation of endothelial NO synthase. NO is a potent vasodilator that increases vascular wall permeability. High NO levels may be an indirect marker confirming the activity of the kinin–kallikrein system, thereby supporting the pathogenesis of AE.

6. The role of involved pro-inflammatory cytokines is also considered: IL-6, TNF- α , IL-1 β .

Regarding the features of AE caused by ACE inhibitors, the following warrant special attention:

1. An increased risk is observed in elderly patients (>65 years) with a history of drug allergy and/or seasonal allergies.

2. A history of tobacco use is associated with an increased risk, as damage to the vascular endothelium promotes significant accumulation of bradykinin. Smokers, particularly those taking ACE inhibitors (enalapril, lisinopril), are at higher risk of bradykinin-mediated AE.

3. Oedema in deeper tissues of the digestive tract as an initial manifestation is a risk factor for a severe course.

4. Patients with AE during ACE inhibitor therapy more frequently have a history of hypersensitivity reactions to nonsteroidal anti-inflammatory drugs (9.2% vs 4.2%, $p < 0.001$).

5. Episodes of angioedema occur more frequently within the first year after initiation of treatment, and their frequency may remain relatively constant over a prolonged period.

6. Oedema of the organs of the digestive tract induces pain of such severity, together with prominent accompanying symptoms, that it simulates acute abdomen and frequently results in unnecessary laparotomies.

7. HAE should be routinely included in the differential diagnostic evaluation of recurrent abdominal pain of unclear aetiology. The clinical relevance of abdominal syndrome in hereditary angioedema is highlighted by the observation that abdominal pain attacks occur in 93% of affected patients and may represent the initial manifestation of the disease.

Conclusions

1. Patients with insulin-dependent diabetes mellitus exhibit a 2.9-fold higher incidence of hypersensitivity

reactions compared with other therapeutic patients, with frequency directly correlating with disease duration and severity.

2. Differentiation between histamine-mediated and bradykinin-mediated angioedema constitutes a critical aspect of clinical practice. A markedly increased risk of angioedema during ACE inhibitor therapy has been demonstrated in patients with a positive allergic history. Failure of angioedema to respond to antihistamines and corticosteroids should raise suspicion of a bradykinin-mediated aetiology.

3. Immediate discontinuation of ACE inhibitor therapy is required, with subsequent replacement by an antihypertensive agent from a different pharmacological class.

4. Knowledge of rare causes of acute abdominal pain expands the differential diagnostic spectrum for surgeons, thereby enabling avoidance of unnecessary interventions. C1-esterase inhibitor deficiency should be excluded in cases presenting with isolated angioedema of the small intestine.

5. Anaesthesiologists must be informed of potential adverse intraoperative reactions in patients on long-term treatment with certain antihypertensive medications.

6. Mandatory professional nutritional education, prevention of polypharmacy, and meticulous recording of documented hypersensitivity reactions in patient records at all levels of care are recommended as integral components of the preventive measures programme.

References:

- Khan DA, Banerji A, Blumenthal KG, Phillips EJ, Solensky R, White AA, et al. Drug allergy: A 2022 practice parameter update. *J Allergy Clin Immunol.* 2022;150(6):1333-93. DOI: <http://doi.org/10.1016/j.jaci.2022.08.028> PMID: 36122788.
- Pallardy M, Bechara R, Whritenour J, Mitchell-Ryan S, Herzyk D, Lebrec H, et al. Drug hypersensitivity reactions: review of the state of the science for prediction and diagnosis. *Toxicol Sci.* 2024;200(1):11-30. DOI: <http://doi.org/10.1093/toxsci/kfae046> PMID: 38588579; PMCID: PMC11199923.
- Cardona V, Ansotegui IJ, Ebisawa M, El-Gamal Y, Fernandez Rivas M, Fineman S, et al. World allergy organization anaphylaxis guidance 2020. *World Allergy Organ J.* 2020;13(10):100472. DOI: <http://doi.org/10.1016/j.waojou.2020.100472> PMID: 33204386; PMCID: PMC7607509.
- Hébert J, Boursiquot JN, Chapdelaine H, Laramée B, Desjardins M, Gagnon R, et al. Bradykinin-induced angioedema in emergency department. *Int J Emerg Med.* 2022;15(1):15. DOI: <http://doi.org/10.1186/s12245-022-00408-6> PMID: 35350995; PMCID: PMC8966254.
- Briggs B, Cline D, Husain I. Disposition of emergency department patients presenting with angiotensin-converting enzyme inhibitor-induced angioedema. *Int J Emerg Med.* 2025;18(1):11. DOI: <http://doi.org/10.1186/s12245-024-00772-5> PMID: 39794708; PMCID: PMC11724552.
- Gülbahar O. Angioedema without wheals: a clinical update. *Balkan Med J.* 2021;38(2):73-81. DOI: <http://doi.org/10.5152/balkanmedj.2021.20060> PMID: 33593719; PMCID: PMC8909242.
- Hahn J, Greve J, Bas M, Kojda G. Bradykinin-Mediated Angioedema Induced by Commonly Used Cardiovascular Drugs. *Drugs and Drug Candidates.* 2023;2(3):708-27. DOI: <https://doi.org/10.3390/ddc2030036>
- Montinaro V, Cicardi M. ACE inhibitor-mediated angioedema. *Int Immunopharmacol.* 2020;78:106081. DOI: <http://doi.org/10.1016/j.intimp.2019.106081> PMID: 31835086. 10
- StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023[update 2025 Jan; cited 2026 Jan 6]. Abdulkarim A, Craig TJ. Hereditary Angioedema. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK482266>
- Suffritti C, Chan S, Ferrara AL, Lekli E, Palestra F, Tuncay G, et al. Bradykinin-Mediated Angioedema Induced by Drugs. *J Clin Med.* 2025;14(16):5712. DOI: <http://doi.org/10.3390/jcm14165712> PMID: 40869540; PMCID: PMC12386469.
- Papapostolou N, Gregoriou S, Katoulis A, Makris M. Five-Membered Nitrogen Heterocycles Angiotensin-Converting Enzyme (ACE) Inhibitors Induced Angioedema: An Underdiagnosed Condition. *Pharmaceuticals (Basel).* 2024;17(3):360. DOI: <http://doi.org/10.3390/ph17030360> PMID: 38543146; PMCID: PMC10974338.
- Jayasinghe M, Caldera D, Prathiraja O, Jena R, Coffie-Pierre JA, Agvei J, et al. A Comprehensive Review of Bradykinin-Induced Angioedema Versus Histamine-Induced Angioedema in the Emergency Department. *Cureus.* 2022;14(11): e32075. DOI: <http://doi.org/10.7759/cureus.32075> PMID: 36600855; PMCID: PMC9803396.
- Lima H, Zheng J, Wong D, Wasserman S, Sussman GL. Pathophysiology of bradykinin and histamine mediated angioedema. *Front Allergy.* 2023;4:1263432. DOI: <http://doi.org/10.3389/falgy.2023.1263432> PMID: 37920409; PMCID: PMC10619149.
- Rubin S, Tomaszewski M. Prediction and prevention of ACE-inhibitor-induced angioedema – an unmet clinical need in management of hypertension. *Hypertens Res.* 2024;47(2):257-60. DOI: <http://doi.org/10.1038/s41440-023-01491-9> PMID: 37945891.
- Nishad M, Verma S, Maqsood R, Pal RS. Etiology, Recent Advances, and Clinical Trials Data for the Treatment of Angioedema: A Review. *Rev Recent Clin Trials.* 2025;20(2):79-95. DOI: <http://doi.org/10.2174/0115748871307432240930051749> PMID: 39400012.
- Reshef A, Buttgerit T, Betschel SD, Caballero T, Farkas H, Grumach AS, et al. Definition, acronyms, nomenclature, and classification of angioedema (DANCE): AAAAI, ACAAI, ACARE, and APAAACI DANCE consensus. *J Allergy Clin Immunol.* 2024;154(2):398-411.e1. DOI: <http://doi.org/10.1016/j.jaci.2024.03.024> PMID: 38670233.
- Pines JM, Poarch K, Hughes S. Recognition and Differential Diagnosis of Hereditary Angioedema in the Emergency Department. *J Emerg Med.* 2021;60(1):35-43. DOI: <http://doi.org/10.1016/j.jemermed.2020.09.044> PMID: 33218838.

Prospects for further research. Further research should focus on elucidating the pathogenetic mechanisms of bradykinin-mediated angioedema in patients with comorbidities. Expansion of clinical observations is warranted to establish additional prognostic criteria for the risk of severe reactions during ACE inhibitor therapy and to refine algorithms for the differential diagnosis and prevention of hypersensitivity reactions.

Contribution of co-authors to the preparation of materials for the scientific article: N. Kaspruk – conceptualization, methodology, planning, material collection, research, analysis of results, original draft writing; S. Batranovska – planning, analysis of results, original draft writing, design, reviewing and editing; S. Melnychuk – methodology, analysis of results, reviewing and editing; T. Kopchuk – analysis of results, preparation for printing; T. Unguryan – analysis of results, preparation for printing; A. Petryuk – material collection, preparation for printing.

Conflict of interest: No conflict of interest was declared by the authors.

Use of Artificial Intelligence. No artificial intelligence was used in the preparation of the manuscript.

Funding sources: This study was self-funded.

18. Bernstein JA, Cremonesi P, Hoffmann TK, Hollingsworth J. Angioedema in the emergency department: a practical guide to differential diagnosis and management. *Int J Emerg Med.* 2017;10(1):15. DOI: <http://doi.org/10.1186/s12245-017-0141-z> PMID: 28405953; PMCID: PMC5389952.
19. Mathey CM, Maj C, Eriksson N, Krebs K, Westmeier J, David FS, et al. Meta-analysis of ACE inhibitor-induced angioedema identifies novel risk locus. *J Allergy Clin Immunol.* 2024;153(4):1073-82. DOI: <http://doi.org/10.1016/j.jaci.2023.11.921> PMID: 38300190.
20. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009;62(10):1006-12. DOI: <http://doi.org/10.1016/j.jclinepi.2009.06.005> PMID: 19631508.
21. Grumach AS, Veronez CL, Csuka D, Farkas H. Angioedema Without Wheals: Challenges in Laboratorial Diagnosis. *Front Immunol.* 2021;12:785736. DOI: <http://doi.org/10.3389/fimmu.2021.785736> PMID: 34956216; PMCID: PMC8694242.
22. Cordonnier DJ, Zaoui P, Halimi S. Role of ACE inhibitors in patients with diabetes mellitus. *Drugs.* 2001;61(13):1883-92. DOI: <http://doi.org/10.2165/00003495-200161130-00001> PMID: 11708761.
23. Knock GA, Poston L. Bradykinin-mediated relaxation of isolated maternal resistance arteries in normal pregnancy and preeclampsia. *Am J Obstet Gynecol.* 1996;175(6):1668-74. DOI: [http://doi.org/10.1016/s0002-9378\(96\)70123-0](http://doi.org/10.1016/s0002-9378(96)70123-0) PMID: 8987958.
24. Kadar L, Kivity S. Urticaria and Angioedema in Pregnancy. *Curr Derm Rep.* 2013;2:236-42. DOI: <https://doi.org/10.1007/s13671-013-0061-y>
25. Stanhewicz AE, Nuckols VR, Pierce GL. Maternal microvascular dysfunction during preeclamptic pregnancy. *Clin Sci (Lond).* 2021;135(9):1083-101. DOI: <http://doi.org/10.1042/CS20200894> PMID: 33960392; PMCID: PMC8214810.

ДЕЯКІ ОСОБЛИВОСТІ АЛЕРГІЧНИХ РЕАКЦІЙ У ХВОРИХ НА ПОЄДНАНУ ПАТОЛОГІЮ: БРАДИКИНІН-ОПОСЕРЕДКОВАНІ РЕАКЦІЇ

Н. М. Каспрук, С. О. Батрановська, С. П. Мельничук, Т. Г. Кончук, Т. М. Унгурян, А. Є. Петрюк

**Буковинський державний медичний університет
(м. Чернівці, Україна)**

Резюме.

Фармакологічна гіперчутливість викликає незадовільні терапевтичні результати при будь-якій супутній патології. Проблема поєднання алергопатології та ендокринопатії стає все більш актуальною, що зумовлено як розповсюдженістю ендокринопатій так і прогресуванням алергічних реакцій в загальному серед населення. Зі збільшенням застосування інгібіторів ангіотензинперетворювального ферменту (АПФ) зростає частота виникнення ангіоневротичного набряку. Диференціація різних варіантів ангіоневротичного набряку є важливою складовою діагностики.

Метою дослідження було провести аналіз особливостей реакцій гіперчутливості у хворих на цукровий діабет, вивчити особливості перебігу випадків ангіоневротичних набряків, покращити діагностику, прогнозування та профілактику патології.

Вважаємо за потрібне привернути увагу лікарів терапевтичного та хірургічного профілів на особливості перебігу випадків ангіоневротичних набряків на тлі базової терапії інгібіторами АПФ.

Матеріали та методи. Проаналізовані амбулаторні карти, історій хвороб 188 пацієнтів, хворих на цукровий діабет із зафіксованими в документації епізодами реакцій, що трактували, як алергічні (основна група) та 122 пацієнтів стаціонару обласної клінічної лікарні з подібними процесами без діабету за 10 років (2015-2024 рр.). Серед основної групи виділена підгрупа з реакціями гіперчутливості, що проявлялися ангіоневротичними набряками та/або гострою кропив'ячкою – 48 пацієнтів. Також проаналізовані дані анкет-опитувальників пацієнтів, які звертались за консультативною допомогою на кафедру клінічної імунології, алергології та ендокринології за вказаний період часу. Методи дослідження: загальноклінічні, біохімічні, імуноферментні, інструментальні, статистично-аналітичні. Дослідження проведено з дотриманням основних принципів біоетики відповідно до положень Гельсінської декларації Всесвітньої медичної асоціації. Аналіз клінічних даних здійснювався ретроспективно на основі медичної документації та анкет-опитувальників. Пацієнти, які проходили анкетування та консультативне обстеження, надали інформовану згоду на використання отриманих даних у науково-дослідницькій роботі. Усі персональні дані пацієнтів були деперсоналізовані та використані виключно з науковою метою. Дослідження не передбачало додаткових інвазивних втручань та не створювало жодних ризиків для здоров'я пацієнтів. Статистичну обробку результатів проводили з використанням методів описової та порівняльної статистики. Дані наведені у вигляді абсолютних та відносних величин (%). Порівняння показників між групами здійснювали з урахуванням клінічних та анамnestичних характеристик. Кореляційний аналіз застосовували для оцінки зв'язку між тривалістю цукрового діабету та частотою реакцій гіперчутливості. Статистично значущими вважали результати при $p < 0,05$.

Дослідження виконано в рамках пілотного проекту. На етапі подальших досліджень проект передбачає розширення вибірки та уточнення отриманих результатів.

Результати дослідження. Давність захворювання діабетом хворих, які включені в дослідження, була від одного до 30 років. Інсулінозалежний діабет діагностований у 82% пацієнтів. Анамnestичні дані щодо наявності реакцій гіперчутливості на лікарські засоби та харчові продукти хворих із інсулінозалежним діабетом були позитивні майже в 3 рази частіше, ніж в контрольній групі, що корелювало із давністю захворювання. За останні роки (2017-2024 рр.) спостерігали зміни й у загальній структурі гіперергій у порівнянні із попередньо аналізованим періодом (2014-2016 рр.). Виявили зміну акцентів в сторону збільшення випадків, що корелювали саме з медикаментозною гіперчутливістю, частіше алергічні реакції у хворих на ЦД були пов'язані із прийомом аналогових препаратів інсуліну, антибіотиків, місцевих анестетиків, рентгенконтрастних речовин, кардіологічних препаратів. Серед лікарських засобів, на які виявлена підвищена чутливість, або є анамnestичні відомості про них, частотний розподіл виглядає наступним чином: препарати інсулінів – 22,7%; засоби, що впливають на систему травлення та метаболічні процеси – 23,17%; антибіотики – 20,5%; нестероїдні протизапальні засоби – 9,7%; препарати кардіогрупи – 9,1%; вітаміни – 3,6%; фітоформи – до 2%. В результаті поглибленого обстеження хворих з епізодами ангіоневротичного набряку проаналізовані випадки, зокрема, що асоціювалися з вживання лізіноприлу в 55- та 70-річній жінок, які проявлялися болем у животі (в другому випадку додатково з блюванням та діареєю). Результати комп'ютерної томографії виявили набряк стінки тонкої кишки. Після відміни препарату епізоди набряку не повторювалися впродовж року. Епізоди асиметричного АН на обличчі у двох чоловіків 62 та 68 років – на фоні прийому раміприлу (алергологічний анамнез не обтяжений), також чоловіків 59 та 75 років з виразним генералізованим свербіжем шкіри без висипань, але ізольованими асиметричними набряками кінцівок на фоні прийомів сна-

лаприлу. Після повної відмови від застосування препаратів з групи інгібіторів АПФ спостерігали регрес симптомів в інтервалі від 1 тижня до 2 місяців. У 4-х з 6-и описаних випадків спостерігалась додатково фотосенсибілізація та гіперестезія шкіри.

Висновки. 1. Частота гіперергічних реакцій у хворих з інсулінозалежним діабетом в 2,9 разів перевищує таку для інших хворих терапевтичного профілю, прямо пропорційна часу виникнення та важкості захворювання. 2. У клінічній практиці важливо диференціювати гістамін-індукований ангіоневротичний набряк від брадикінін-опосередкованого. Пацієнти з позитивним алергоанамнезом мають підвищений ризик виникнення ангіоневротичного набряку при застосуванні інгібіторів АПФ. Якщо пацієнт із ангіоневротичним набряком «не дає відповіді» на антигістамінні та **кортикостероїди**, необхідно запідозрити брадикінін-опосередкований ангіоневротичний набряк. 3. Терапію інгібіторами АПФ слід негайно припинити та замінити засобом, що належить до іншої групи гіпотензивних препаратів. 4. Знання рідкісних причин гострого абдомінального болю дозволяє хірургам розширити спектр диференціальної діагностики та уникнути невиправданих втручань. У випадках ангіоневротичного набряку лише тонкої кишки важливо виключити дефіцит інгібіторів С1-естерази. 5. Анестезіологи повинні знати про такі побічні реакції, що можуть виникати у пацієнтів інтраопераційно на фоні базового прийому деяких гіпотензивних засобів. 6. Програма профілактичних заходів повинна включати обов'язкову професійну дієтологічну освіту хворих, запобігання поліпрагмазії та ретельну фіксацію даних про виявлені реакції гіперчутливості в медичній документації хворих на всіх рівнях.

Ключові слова: інгібітори АПФ; цукровий діабет; побічна дія; ангіоневротичний набряк; брадикінін.

Contact information:

N. Kaspruk – Candidate of Medical Sciences, Associate Professor, Department of Clinical Immunology, Allergology and Endocrinology Bukovinian State Medical University (Chernivtsi, Ukraine)

e-mail: kaspruk.natalia@bsmu.edu.ua

ORCID ID: <https://orcid.org/0000-0001-9956-0574>

Scopus Author ID: <https://www.scopus.com/authid/detail.uri?authorId=58401072800>

Researcher ID: <https://www.webofscience.com/wos/author/record/D-5469-2017>

S. Batranovska – Teacher of the BSMU Vocational College at the Department of Pharmacology Bukovinian State Medical University (Chernivtsi, Ukraine)

e-mail: batranovska.svitlana@bsmu.edu.ua

ORCID ID: <https://orcid.org/0000-0003-2822-7314>

Researcher ID: <https://www.webofscience.com/wos/author/record/PIJ-1915-2026>

S. Melnychuk – Candidate of Medical Sciences, Associate Professor, Department of Pharmacology Bukovinian State Medical University (Chernivtsi, Ukraine)

e-mail: pasevich.svitlana@bsmu.edu.ua

ORCID ID: <https://orcid.org/0000-0002-8784-178X>

Scopus Author ID: <https://www.scopus.com/authid/detail.uri?authorId=57203509732>

Researcher ID: <https://www.webofscience.com/wos/author/record/C-6942-2017>

T. Kopchuk – Candidate of Medical Sciences, Associate Professor, Department of Pharmacology Bukovinian State Medical University (Chernivtsi, Ukraine)

e-mail: kopchuk.tamara@bsmu.edu.ua

ORCID ID: <https://orcid.org/0000-0001-5547-0243>

Scopus Author ID: <https://www.scopus.com/authid/detail.uri?authorId=57202743875>

Researcher ID: <https://www.webofscience.com/wos/author/record/C-4380-2017>

T. Unhuryan – Candidate of Medical Sciences, Teacher of the Vocational College at the Department of Pharmacology Bukovinian State Medical University (Chernivtsi, Ukraine)

e-mail: unhuryan.tetyana@bsmu.edu.ua

ORCID ID: <https://orcid.org/0000-0001-5872-2178>

Scopus Author ID: <https://www.scopus.com/authid/detail.uri?authorId=57215721386>

Researcher ID: <https://www.webofscience.com/wos/author/record/C-4448-2017>

A. Petriuk – Candidate of Medical Sciences, Teacher of the Vocational College at the Department of Pharmacology Bukovinian State Medical University (Chernivtsi, Ukraine)

e-mail: Petriuk.Anatolii@bsmu.edu.ua

ORCID ID: <https://orcid.org/0000-0003-2789-0579>

Відомості про авторів:

Каспрук Наталія Михайлівна – к.мед.н., доцентка кафедри клінічної імунології, алергології та ендокринології БДМУ (м. Чернівці, Україна)

e-mail: kaspruk.natalia@bsmu.edu.ua

ORCID ID: <https://orcid.org/0000-0001-9956-0574>

Scopus Author ID: <https://www.scopus.com/authid/detail.uri?authorId=58401072800>

Researcher ID: <https://www.webofscience.com/wos/author/record/D-5469-2017>

Батрановська Світлана Олександрівна – викладачка фахового коледжу на кафедрі фармакології БДМУ (м. Чернівці, Україна)

e-mail: batranovska.svitlana@bsmu.edu.ua

ORCID ID: <https://orcid.org/0000-0003-2822-7314>

Researcher ID: <https://www.webofscience.com/wos/author/record/PIJ-1915-2026>

Мельничук Світлана Петрівна – к.мед.н., доцентка кафедри фармакології БДМУ (м. Чернівці, Україна)

e-mail: pasevich.svitlana@bsmu.edu.ua

ORCID ID: <https://orcid.org/0000-0002-8784-178X>

Scopus Author ID: <https://www.scopus.com/authid/detail.uri?authorId=57203509732>

Researcher ID: <https://www.webofscience.com/wos/author/record/C-6942-2017>

Копчук Тамара Григорівна – к.мед.н., доцентка кафедри фармакології БДМУ (м. Чернівці, Україна)

e-mail: kopchuk.tamara@bsmu.edu.ua

ORCID ID: <https://orcid.org/0000-0001-5547-0243>

Scopus Author ID: <https://www.scopus.com/authid/detail.uri?authorId=57202743875>

Researcher ID: <https://www.webofscience.com/wos/author/record/C-4380-2017>

Унгурян Тетяна Миколаївна – к.мед.н., викладачка фахового коледжу БДМУ на кафедрі фармакології БДМУ (м. Чернівці, Україна)

e-mail: unhuryan.tetyana@bsmu.edu.ua

ORCID ID: <https://orcid.org/0000-0001-5872-2178>

Scopus Author ID: <https://www.scopus.com/authid/detail.uri?authorId=57215721386>

Researcher ID: <https://www.webofscience.com/wos/author/record/C-4448-2017>

Петрюк Анатолій Євгенович – к.мед.н., викладач фахового коледжу БДМУ на кафедрі фармакології БДМУ (м. Чернівці, Україна)

e-mail: Petriuk.Anatolii@bsmu.edu.ua

ORCID ID: <https://orcid.org/0000-0003-2789-0579>

Received by the editorial office: 06 December 2025.

Approved for publication: 23 February 2026.

Published: 27 March 2026.

