DOI: 10.17816/KMJ340788

# Features of the course of type 1 diabetes mellitus and its complications against the background of undifferentiated connective tissue dysplasia

S.I. Mazepa*, E.F. Kotovshchikova, I.A. Veitsman, N.A. Lomakina, M.N. Nechaeva

Altai State Medical University, Barnaul, Russia

## Abstract

Changes in connective tissue against the background of hyperglycemia in patients with type 1 diabetes mellitus is a morphological substrate for the formation of diabetic complications. The presence of undifferentiated connective tissue dysplasia in a patient with absolute insulin deficiency, the prevalence of individual external manifestations of which among young people is 85.4%, can increase the risk of developing and progressing complications of diabetes mellitus. The purpose of the review is to summarize the literature data on the impact of undifferentiated connective tissue dysplasia on the course of type 1 diabetes mellitus and its complications when they are combined in one patient. An analysis of the literature has shown that today there are single studies that have studied the specifics of the course of type 1 diabetes mellitus and its complications against the background of undifferentiated connective tissue dysplasia, with some aspects analyzed in children and adolescents, others in adults, which does not allow to draw clear conclusions. The results of these studies demonstrated earlier development and progression of such diabetic complications as nephropathy, neuropathy, post-injection lipodystrophy in patients with increased dysplastic stigma. According to some experts, patients with type 1 diabetes mellitus and concomitant undifferentiated connective tissue dysplasia should be allocated to a separate group of dispensary observation, since they may have a higher risk of developing and progressing rate of chronic complications of diabetes mellitus, which leads to a concomitant decrease in quality of life and increased risk of disability. However, to date, the question of the influence of increased dysplastic stigmatization on the course of type 1 diabetes mellitus has not been fully studied.

**Keywords**: undifferentiated connective tissue dysplasia, dysplastic stigma, type 1 diabetes mellitus, diabetic complications, review.

**For citation**: Mazepa SI, Kotovshchikova EF, Veitsman IA, Lomakina NA, Nechaeva MN. Features of the course of type 1 diabetes mellitus and its complications against the background of undifferentiated connective tissue dysplasia. *Kazan Medical Journal.* 2023;104(6):877–884. DOI: 10.17816/KMJ340788.

## Introduction

Signs of connective tissue dysplasia are observed in one out of every six Russian inhabitants, and 85.4% of young people exhibit individual external manifestations of connective tissue dysmorphogenesis [1]. Currently, researchers are intensively exploring the issue of undifferentiated connective tissue dysplasia (UCTD) [2].

Diabetes mellitus (DM) is a significant medical and social problem that affects over 537 million adults worldwide, with 47% experiencing complications [3–6].

According to I.S. Maslova and V.E. Kenner, the probability rates of simultaneous presence of type 1 DM (T1DM) and UCTD are 40% and 43%, respectively [7, 8]. Both pathologies have a systemic level of lesions and are likely to worsen their course. The influence of UCTD on the DM course and its complications when they coexist in a single patient is currently not fully understood.

Thus, this review aimed to analyze the effect of increased dysplastic stigma on T1DM and the progression of its complications when coexisting in a single patient. Literature sources published from 2005 to 2023 and indexed in eLibrary, Google Scholar, and PubMed were reviewed to investigate the effect of UCTD on the course of T1DM and the progression of its complications when these pathologic processes coexist in a single patient. After analyzing the abstracts for compliance with the review topic, 52 sources were identified using the keywords “connective tissue dysplasia” and “type 1 DM.”

*For correspondence: svetlana-mazepa@yandex.ru

Submitted 08.06.2023; accepted 17.07.2023; published 26.10.2023.

## Connective tissue pathology in patients with T1DM

Connective tissue is the primary morphological substrate for the development of diabetic micro- and macroangiopathies at the tissue level. In patients with DM, collagenopathies can be a direct consequence of carbohydrate metabolism disorders and a manifestation of other comorbidities [9–13].

Chronic hyperglycemia in DM causes metabolic and hemodynamic disorders that affect the metabolism of large molecules in the connective tissue, primarily collagen. Increased collagen and fibrin formation contributes to the thickening of the basement membrane of small vessels and capillaries, such as retinal vessels, renal tubular capillaries, and vasa nervorum. This thickening forms the morphological basis for the development and progression of DM complications [14–16].

Long-term control of hyperglycemia is associated with the prevention of the development and progression of DM complications [17]. Beyond impaired glucose metabolism, metabolic consequences can affect virtually every tissue and organ system [18]. Even in patients with good glycemic control, vascular complications can progress because of "metabolic memory" [19]. High glucose levels can result in microvascular and macrovascular complications that are linked to vision loss, peripheral polyneuropathy, renal failure, myocardial infarction, stroke, and atherosclerosis [20, 21].

Despite improvements in medical care for patients with T1DM, they are still at a higher risk of chronic kidney disease, cardiovascular complications, and premature death than those without absolute insulin deficiency [22–25]. A study reported an increase in collagen synthesis during the initial stages of diabetic nephropathy, indicating a relationship between collagen metabolism disorders and progression of DM complications [24].

In vitro experiments demonstrated that the synthesis of type IV collagen increases 2–3 times at a glucose concentration of 30 mmol/L. However, collagen metabolism did not normalize even after compensation of carbohydrate metabolism and achievement of target glycemic parameters.

Under hyperglycemic conditions, the syntheses of collagen types I and VI increase. The effects of hyperglycemia and glycation products are mediated by protein kinase C and growth factors, such as transforming growth factor and connective tissue growth factor. In addition, angiotensin and endothelin I play a significant role in increased collagen synthesis in diabetic nephropathy. In this case, increased collagen formation in the kidneys decreases the activity of collagenolytic enzymes, which activates collagen glycation and results in the accumulation of excessive collagen, a key factor in the formation and progression of diabetic nephrosclerosis [25].

Increased urinary excretion of type IV collagen and peptide-bound hydroxyproline and the relative activities of collagenolytic enzymes in serum indicate increased collagen formation [23]. In the preclinical stage, urinary excretion of type IV collagen may serve as an early sensitive marker of diabetic nephropathy [25–27].

## Prevalence of undifferentiated connective tissue dysplasia in patients with T1DM

UCTD has a systemic effect on the connective tissue structure. These changes are both qualitative and quantitative [28]. The main etiological factor of this pathology is considered mutations in genes responsible for the formation and organization of collagen, extracellular matrix components, and enzymes involved in collagen metabolism and fibrillogenesis [28, 29].

In addition to gene variability and mutation, environmental factors can also play a significant role in connective tissue disorganization. Risk factors that contribute to UCTD development include chronic fetal hypoxia and the mother's pregnancy course in the presence of chronic diseases, toxicosis, eclampsia, and anemia [30].

Epigenetic factors that influence UCTD development include irrational nutrition (such as macro- and microelement deficiencies, hypovitaminosis, and protein-energy deficiency), unbalanced physical activity, environmental pollution, stress, and climate change [1]. The diversity of clinical signs of connective tissue dysplasia makes them difficult to unify [31].

V.E. Kenner found that 43% of patients diagnosed with DM exhibited several UCTD signs. They also revealed that scoliosis, flat feet, and bleeding gums are the most common minor developmental anomalies among patients with DM [7].

I.S. Maslova et al. discovered that 40% of patients with T1DM exhibited increased dysplastic stigma. They also investigated the prevalence of certain minor developmental anomalies in these patients. Joint hypermobility, flat feet, asthenic body type, increased skin elasticity, varicose veins, internal organ prolapse, height-to-arm span ratio of >1.1, mitral valve prolapse, and renal cysts are the most common signs of dysplasia in patients with absolute insulin deficiency. In patients with T1DM, the rarest UCTD manifestations include gothic palate, chest deformity, biliary tract deformity, and arachnodactyly. The most frequent minor developmental anomalies are the ability to roll the tongue into a tube, myopia, and protruding auricles (Table 1) [8].

**Table 1**. Prevalence of selected dysplastic features in patients with type 1 diabetes mellitus [8]

| Most common UCTD signs in adults with type 1 diabetes mellitus | Most common UCTD signs in children with type 1 diabetes mellitus | Least common UCTD signs in adults with type 1 diabetes mellitus |
|---|---|---|
| Myopia<br>Joint hypermobility<br>Flat feet<br>Asthenic body type<br>Increased skin elasticity<br>Varicose veins<br>Lowering of the internal organs | Scoliosis<br>Flat feet<br>Visible venous network<br>Plantar callosities on the feet | Gothic palate<br>Deformity of the thorax<br>Deformity of the biliary tract<br>Arachnodactyly |

Note: NDST is an undifferentiated connective tissue dysplasia.

In children and adolescents with absolute insulin deficiency, scoliosis is the most common phenotypic sign of dysplasia (70%). The second most common sign is flat feet (60%). Other minor developmental anomalies include a visible venous network and plantar callosities on the feet [21].

**Effect of connective tissue dysplasia on the course of T1DM and its complications**

Currently, few studies have investigated the course of DM in patients with concomitant dysplasia. The comorbidity index in patients with absolute insulin deficiency in combination with UCTD is higher than that in patients without minor developmental anomalies [8].

I.V. Druk et al. found that young patients with UCTD exhibit subclinical manifestations of anxiety and depression [32, 33]. The coexistence of UCTD and DM can negatively affect glycemic control quality, worsen disease compensation [34–38], and accelerate the development and progression of DM complications.

I.L. Alimova et al. investigated the clinical characteristics of T1DM and micro- and macrovascular complications in children and adolescents with concomitant UCTD. The study revealed that compared with patients without UCTD manifestations, those with UCTD manifestations were more likely to develop nephropathy and neuropathy during the first 5 years of the disease course, and the complications had a more severe course. No significant difference in the prevalence of nephropathy and neuropathy was found between patients with and without UCTD when the duration of DM was more than 5 years. Patients with concomitant UCTD showed the most pronounced clinical manifestations of polyneuropathy. The prevalence of DM complications did not correlate with UCTD phenotypes.

Furthermore, I.L. Alimova et al. reported that neuropathy, nephropathy, and lipodystrophia more frequently occur in patients with both UCTD and T1DM than in those without UCTD. However, retinopathy was only present in 11.8% of patients with dysplasia and DM. The authors suggest that this may be due to inadequate ophthalmologic services during the study and potential subjective factors [21].

According to I.A. Kurnikova et al., patients who have both DM and UCTD are at a higher risk of developing diabetic foot syndrome [39].

Autonomic neuropathy is a DM complication [3, 40] caused by the glycation of structural and functional proteins, primarily collagen. The clinical symptoms of diabetic autonomic neuropathy are diverse and may include urogenital, gastrointestinal, cardiovascular manifestations, and sweating disorders [41]. T.E. Chernyshova et al. reported a correlation between the risk of development, rate of progression of diabetic autonomic neuropathy, and degree of dysplastic stigmatization of patients [42].

The gastrointestinal manifestations of diabetic autonomic neuropathy include gastric and intestinal motility disorders, esophageal dyskinesia, cholecystopathy, anorectal dysfunction, and other related conditions [40, 43, 44]. Similarly, UCTD can cause gastroenterological manifestations such as sex development disorders, motor-tonic disorders, and size and fixation problems [45].

I.A. Kurnikova et al. found that congenital changes in collagen metabolism, specifically UCTD, do not significantly affect the risk of digestive pathology in patients with T1DM. The study results indicate that acquired disorders of collagen metabolism play a more significant role in the development of digestive pathologies in patients with absolute insulin insufficiency. These disorders alter the course of DM and worsen glycemic control. Importantly, hypersympathicotonia significantly affects the functional state of the digestive organs, leading to issues with motor evacuation and secretory functions [46].

Cardiovascular autonomic neuropathy is a severe and debilitating underdiagnosed complication of DM. It is characterized by impaired autonomic control of the cardiovascular system [40, 41, 47]. This condition affects 17%–73% of patients with DM, depending on demographic factors [50]. Diabetic cardiovascular autonomic neuropathy

is characterized by several manifestations, including sinus tachycardia at rest without sinus arrhythmia, poor exercise tolerance, painless myocardial ischemia, orthostatic hypotension, sudden cardiac arrest, and sudden death [45, 48].

Connective tissue dysplasia is a significant cause of cardiovascular autonomic neuropathy [51, 52]. T.E. Chernyshova et al. observed that diabetic cardiovascular autonomic neuropathy with UCTD had a rapid progression of hypersympathicotonia, leading to life-threatening manifestations such as *QT* interval prolongation and dispersion, myocardial electrical instability, and "fixed" heart rhythm [42].

Therefore, the coexistence of UCTD and T1DM in a patient may increase the risk of developing cardiovascular autonomic neuropathy and associated mortality. However, whether this is the case remains unanswered.

## Conclusions

The coexistence of connective tissue pathology in UCTD and secondary diabetic modification of the connective tissue structure plays an important role in the formation and progression of DM complications. To date, the limited number of studies that have examined the influence of concomitant UCTD on the course and progression of T1DM have described only certain aspects. Some of these studies have focused on children and adolescents, whereas others have focused on adults. Accordingly, it is difficult to draw definitive conclusions.

Further research is necessary to examine the effect of UCTD on the course of T1DM. This will allow for the analyses of patients with T1DM and UCTD into a separate observation group with more frequent screening for DM complications. This step will help reduce the risk of complications and preserve the quality of life of the patients.

**Authors' contribution**. S.I.M., idea for the manuscript, search for literary sources, writing the article, and editing of the manuscript; I.A.V., scientific advice; N.A.L., editing the text; M.N.N., search for literary sources: E.F.K., co-authorship and approval of the final manuscript.

**Funding source**. The study received no sponsorship support.

**Conflict of interest**. The authors declare no conflict of interest for the submitted article.

## REFERENCES

1. Guidelines of the Russian scientific medical society of internal medicine on the diagnosis, treatment and rehabilitation of patients with the connective tissue dysplasia (first edition). *Medical news of North Caucasus*. 2018;13(1-2):137–209. (In Russ.) DOI: 10.14300/mnnc.2018.13037.

2. Nechaeva GI, Martynov AI. *Sovremennyy podkhod pri displazii soedinitel'noy tkani v kardiologii: diagnostika i lechenie*. Rukovodstvo dlya vrachey. (Modern approach to connective tissue dysplasia in cardiology: diagnosis and treatment. Guide for doctors.) M.: GEOTAR-Media; 2023. p. 13. (In Russ.)

3. Dedov II, Shestakova MV, Mayorova AYu. *Algorithms of specialized medical care for patients with diabetes mellitus. 10th edition*. M.: Rossiyskaya assotsiatsiya endokrinologov; Natsional'nyy meditsinskiy issledovatel'skiy tsentr endokrinologii; 2021. p. 14–15. (In Russ.)

4. Glovaci D, Fan W, Wong ND. Epidemiology of diabetes mellitus and cardiovascular disease. *Curr Cardiol Rep.* 2019;21(4):21. DOI: 10.1007/s11886-019-1107-y.

5. Cloete L. Diabetes mellitus: an overview of the types, symptoms, complications and management. *Nurs Stand.* 2022;37(1):61–66. DOI: 10.7748/ns.2021.e11709.

6. Htay T, Soe K, Lopez-Perez A, Doan AH, Romagosa MA, Aung K. Mortality and cardiovascular disease in type 1 and type 2 diabetes. *Curr Cardiol Rep.* 2019; 21(6):45. DOI: 10.1007/s11886-019-1133-9.

7. Kenner VE. The incidence of mesenchymal dysplasia in patients with type 1 diabetes mellitus. Effect of mesenchymal dysplasia on the course of type 1 diabetes mellitus. *Scientist (Russia).* 2019;(4):13. (In Russ.) EDN: RJDQZD.

8. Maslova IS, Curnicova IA, Kuznetsova IA, Zikina SA, Klimentjeva GI. The rehabilitation forecast at patients with a diabetes mellitus and increased dysplastic stigmation. *Fundamental research.* 2011;(6):112–115. (In Russ.) EDN: NQWOFT.

9. Tuleta I, Frangogiannis NG. Diabetic fibrosis. *Biochim Biophys Acta Mol Basis Dis*. 2021;1867(4):166044. DOI: 10.1016/j.bbadis.2020.166044.

10. Luo XM, Yan C, Feng YM. Nanomedicine for the treatment of diabetes-associated cardiovascular diseases and fibrosis. *Adv Drug Deliv Rev.* 2021;172:234–248. DOI: 10.1016/j.addr.2021.01.004.

11. Juin SK, Pushpakumar S, Tyagi SC, Sen U. Glucosidase inhibitor, Nimbidiol ameliorates renal fibrosis and dysfunction in type 1 diabetes. *Sci Rep.* 2022;12(1):21707. DOI: 10.1038/s41598-022-25848-1.

12. Xu L, Zhang Y, Chen J, Xu Y. Thrombospondin-1: A key protein that induces fibrosis in diabetic complications. *J Diabetes Res.* 2020;2020:8043135. DOI: 10.1155/2020/8043135.

13. Ma T, Dong LJ, Du XL, Niu R, Hu BJ. Research progress on the role of connective tissue growth factor in fibrosis of diabetic retinopathy. *Int J Ophthalmol*. 2018;11(9):1550–1554. DOI: 10.18240/ijo.2018.09.20.

14. Kostov K, Blazhev A. Use of glycated hemoglobin ($A_{1c}$) as a biomarker for vascular risk in type 2 diabetes: Its relationship with matrix metalloproteinases-2, -9 and the metabolism of collagen IV and elastin. *Medicina (Kaunas).* 2020;56(5):231. DOI: 10.3390/medicina56050231.

15. Gatseva A, Sin YY, Brezzo G, Van Agtmael T. Basement membrane collagens and disease mechanisms. *Essays Biochem*. 2019;63(3):297–312. DOI: 10.1042/EBC20180071.

16. Sandler CN, McDonnell ME. The role of hemoglobin $A_{1c}$ in the assessment of diabetes and cardiovascular risk. *Cleve Clin J Med.* 2016;83(5 Suppl 1):S4–S10. DOI: 10.3949/ccjm.83.s1.02.

17. Kohnert KD, Heinke P, Zander E, Vogt L, Salzsieder E. Glycemic key metrics and the risk of diabetes-associated complications. *Rom J Diabetes Nutr Metab Dis.* 2016;(23):403–413. DOI: 10.1515/rjdnmd-2016-0047.

18. Lyons TJ, Basu A. Biomarkers in diabetes: Hemoglobin $A_{1c}$, vascular and tissue markers. *Transl Res.* 2012;(159):303–312. DOI: 10.1016/j.trsl.2012.01.009.

19. Keating ST, van Diepen JA, Riksen NP, El-Osta A. Epigenetics in diabetic nephropathy, immunity and metabolism. *Diabetologia.* 2018;(61):6–20. DOI: 10.1007/s00125-017-4490-1.

20. Qaseem A, Wilt TJ, Kansagara D, Horwitch C, Barry MJ, Forciea MA,, Fitterman N, Balzer K, Boyd C, Humphrey LL, Iorio A, Lin J, Maroto M, McLean R, Mustafa R, Tufte J. Hemoglobin $A_{1c}$ targets for glycemic control with pharmacologic therapy for nonpregnant adults with type 2 diabetes mellitus: A guidance statement update from the American College of Physicians. *Ann Intern Med.* 2018;(168):569–576. DOI: 10.7326/M17-0939.

21. Alimova IL, Pashinskaya NB, Pleskachevskaya TA. Peculiarities of diabetes mellitus type 1 in children and adolescents against the background of connective tissue dysplasia. *Medical news of the North Caucasus.* 2016;(11):271–275. (In Russ.) DOI: 10.14300/mnnc.2016.11053.

22. Pilemann-Lyberg S, Rasmussen DGK, Hansen TW, Tofte N, Winther SA, Holm Nielsen S, Theilade S, Karsdal MA, Genovese F, Rossing P. Markers of collagen formation and degradation reflect renal function and predict adverse outcomes in patients with type 1 diabetes. *Diabetes Care.* 2019;42(9):1760–1768. DOI: 10.2337/dc18-2599.

23. Genovese F, Manresa AA, Leeming DJ, Karsdal MA, Boor P. The extracellular matrix in the kidney: A source of novel non-invasive biomarkers of kidney fibrosis? *Fibrogenesis Tissue Repair.* 2014;7(1):4. DOI: 10.1186/1755-1536-7-4.

24. Klimontov VV, Eremenko NV, Myakina NE, Fazullina ON. Cystatin c and collagen type iv in diagnostics of chronic kidney disease in type 2 diabetic patients. *Diabetes mellitus.* 2015;(1):87–93. (In Russ.) DOI: 10.14341/DM2015187-93.

25. Bondar IA, Klimontov VV. Collagen metabolic changes in diabetic nephropathy. *Problems of Endocrinology.* 2005;51(2):23–28. (In Russ.) DOI: 10.14341/probl200551223-28.

26. Bondar IA, Klimontov VV, Parfentyeva EM, Romanov VV, Nadeev AP. Urinary excretion of type IV collagen as an early marker of renal fibrosis in patients with diabetes mellitus. *Diabetes mellitus.* 2011;(4):29–31. (In Russ.) DOI: 10.14341/2072-0351-5813.

27. Kalmykova AS, Abdullina AE. Role of type IV collagen in the development of diabetic nephropathy in patients with diabetes mellitus. *Medical news of the North Caucasus.* 2020;(4):600–604. (In Russ.) DOI: 10.14300/mnnc.2020.15143.

28. Maslova IS, Kurnikova IA. Peculiarities of diabetes mellitus in combination with connective tissue disorders. *Fundamental research*. 2010;(8):41–45. (In Russ.) EDN: MUVVCX.

29. Rumyantseva VA, Zaklyazminskaya EV. Clinical and genetic diversity of hereditary connective tissue dysplasia. *Clinical and experimental surgery. Petrovsky journal.* 2015;2(8): 2015;2(8):5–17. (In Russ.) EDN: UMAUVL.

30. Kalaeva GYu, Khokhlova OI, Deev IA, Mikheenko GA. Risk factors associated with the development of undifferentiated connective tissue dysplasia. *Bulletin of Siberian Medicine.* 2018;(2):41–48. (In Russ.) DOI: 10.20538/1682-0363-2018-2-41-48.

31. Kil'diyarova RR, Nechaeva GI, Chernyshova TE. *Displaziya soedinitel'noy tkani*. (Connective tissue dysplasia.) M.: GEOTAR-Media; 2020. p. 27–28. (In Russ.)

32. Druk IV, Loginova EN, Vershinina MV, Lyalyukova EA, Drokina OV. Features of the psychological status of persons of young age with connective tissue dysplasia. *Omskiy psikhiatricheskiy zhurnal*. 2019;(3):5–9. (In Russ.) EDN: ZDAXDG.

33. Galeeva VR. The psychological state of young people with undifferentiated connective tissue dysplasia. *Scientist (Russia).* 2022;(4):179–180. (In Russ.) EDN: TYEMGN.

34. Yunilaynen OA. Anxiety disorders in patients with diabetes mellitus. *Effektivnaya farmakoterapiya.* 2016;(37):18–24. (In Russ.) EDN: XWUOTV.

35. Buchberger B, Huppertz H, Krabbe L, Lux B, Mattivi JT, Siafarikas A. Symptoms of depression and anxiety in youth with type 1 diabetes: A systematic review and meta-analysis. *Psychoneuroendocrinology.* 2016;70:70–84. DOI: 10.1016/j.psyneuen.2016.04.019.

36. Franquez RT, de Souza IM, Bergamaschi CC. Interventions for depression and anxiety among people with diabetes mellitus: Review of systematic reviews. *PLoS One.* 2023;18(2):e0281376. DOI: 10.1371/journal.pone.0281376.

37. Liu X, Haagsma J, Sijbrands E, Buijks H, Boogaard L, Mackenbach JP, Erasmus V, Polinder S. Anxiety and depression in diabetes care: Longitudinal associations with health-related quality of life. *Sci Rep.* 2020;10(1):8307. DOI: 10.1038/s41598-020-57647-x.

38. Chopera P, Mbambo SG, Matsungo TM. Relationships of depression and anxiety to readmission rates among patients with diabetes from Harare and Parirenyatwa referral hospitals in Zimbabwe. *Afr Health Sci.* 2021;21(3):1291–1300. DOI: 10.4314/ahs.v21i3.40.

39. Kurnikova IA, Chernishova TE, Klimentieva GI, Maslova IS. Collagen metabolism in the risk assessment of development of diabetic foot syndrome. *Siberian medical journal.* 2011;(3-2):106–108. (In Russ.) EDN: OFXMOL.

40. Feldman EL, Callaghan BC, Pop-Busui R, Zochodne DW, Wright DE, Bennett DL, Bril V, Russell JW, Viswanathan V. Diabetic neuropathy. *Nat Rev Dis Primers.* 2019;5(1):41. DOI: 10.1038/s41572-019-0092-1.

41. Strokov IA, Zilov AV, Al'bekova ZhS, Fokina AA. Diabetic autonomic cardiovascular neuropathy. *Russkiy meditsinskiy zhurnal*. 2011;(30):1874–1877. (In Russ.) EDN: QZIZJL.

42. Kotov SV, Rudakova IG, Isakova EV, Volchenkova TV. Diabetic neuropathy: a variety of clinical forms (lecture). *RMJ. Medical review.* 2017;25(11):822–830. (In Russ.)

43. Chernyshova TE, Curnikova IA, Maslova IS. Connective tissue dysplasia: prognostic significance in diabetologia. *Kubanskiy nauchnyy meditsinskiy vestnik*. 2009;(6):76–79. (In Russ.) EDN: KWJIAP.

44. Kurniawan AH, Suwandi BH, Kholili U. Diabetic gastroenteropathy: A complication of diabetes mellitus. *Acta Med Indones*. 2019;51(3):263–271. PMID: 31699951.

45. Aleksandrova MR, Martyukova AV. Connective tissue dysplasia and gastroenterological pathology. Points of contact. *Bulletin of medical internet conferences.* 2019;(9):396. (In Russ.) EDN: PCCZTW.

46. Kurnikova IA, Klimentyeva GI, Maslova IS. To the problem of the influence of connective tissue dysplasia on the risk of gastrointestinal diseases in patients with diabetes. *Siberian medical journal*. 2011;26(3-2):71–74. (In Russ.) EDN: OFXMKP.

47. Agashe S, Petak S. Cardiac autonomic neuropathy in diabetes mellitus. *Methodist Debakey Cardiovasc J.* 2018;14(4):251–256. DOI: 10.14797/mdcj-14-4-251.

48. Alimova IL. Diabetic cardiovascular autonomous neuropathy in children and adolescents. *Vestnik Smolenskoy gosudarstvennoy meditsinskoy akademii*. 2020;(1):196–210. (In Russ.) EDN: CYXKCH.

49. Dimitropoulos G, Tahrani AA, Stevens MJ. Cardiac autonomic neuropathy in patients with diabetes mellitus. *World J Diabetes*. 2014;5(1):17–39. DOI: 10.4239/wjd.v5.i1.17.

50. Williams S, Raheim SA, Khan MI, Rubab U, Kanagala P, Zhao SS, Marshall A, Brown E, Alam U. Cardiac autonomic neuropathy in type 1 and 2 diabetes: Epidemiology, pathophysiology, and management. *Clin Ther*. 2022;44(10):1394–1416. DOI: 10.1016/j.clinthera.2022.09.002.

51. Smetanin MYu, Chernyshova TE, Pimenov LT, Kononova NYu. Autonomic dysfunction as a manifestation of connective tissue dysplasia in women. *Medical news of the North Caucasus.* 2018;13(4):594–596. (In Russ.) DOI: 10.14300/mnnc.2018.13112.

52. Smetanin MYu, Loginova EN. Dysplastic heart. Left ventricular myocardial deformation in undifferentiated connective tissue dysplasia (literature review). *Prakticheskaya meditsina*. 2022;20(5):13–18. (In Russ.) EDN: GWIZPE.

## Author details

**Svetlana I. Mazepa**, Assist., Depart. of Propaedeutics of Internal Diseases named after Prof. Z.S. Barkagan, Altai State Medical University, Barnaul, Russia; svetlana-mazepa@yandex.ru; ORCID: https://orcid.org/0000-0002-3232-85400

**Elena F. Kotovshchikova**, M.D., D. Sci. (Med.), Prof., Depart. of Propaedeutics of Internal Diseases named after Prof. Z.S. Barkagan, Altai State Medical University, Barnaul, Russia; kotov-l@mail.ru; ORCID: https://orcid.org/0000-0002-3246-5609

**Inna A. Veitsman**, M.D., Cand. Sci. (Med.), Assoc. Prof., Depart. of Propaedeutics of Internal Diseases named after Prof. Z.S. Barkagan, Altai State Medical University, Barnaul, Russia; inna_veits@mail.ru; ORCID: https://orcid.org/0000-0001-5826-1068

**Natalia A. Lomakina**, M.D., Cand. Sci. (Med.), Depart. of Propaedeutics of Internal Diseases named after Prof. Z.S. Barkagan, Altai State Medical University, Barnaul, Russia; darij.85@mail.ru; ORCID: https://orcid.org/0000-0002-1237-526X

**Mariya N. Nechaeva**, Stud., Institute of Clinical Medicine, Altai State Medical University, Barnaul, Russia; nelostons@gmail.com; ORCID: https://orcid.org/0000-0003-4837-1444