

RAMAZ KURASHVILI ^{1,2}, ELENA SHELESTOVA ^{1,3}

THE ROLE OF TRADITIONAL AND EMERGING RISK FACTORS
IN THE DEVELOPMENT OF DIABETES MELLITUS

¹ National Center for Diabetes Research; ²European University;

³ Georgian National University SEU; Tbilisi, Georgia

Doi: <https://doi.org/10.52340/jecm.2024.05.06>

რამაზ კურაშვილი ^{1,2}, ელენე შელესტოვა ^{1,3}

ტრადიციული და ახალი რისკის ფაქტორების როლი შაქრიანი დიაბეტის განვითარებაში

¹დიაბეტის კვლევის ეროვნული ცენტრი, ²ევროპის უნივერსიტეტი,

³საქართველოს ეროვნული უნივერსიტეტი/სეუ; თბილისი, საქართველო

რეზიუმე

შაქრიანი დიაბეტი (შდ) ქრონიკული მდგომარეობაა, რომელიც ხასიათდება ჰიპერგლიკემიით. შდ-ით დაავადებულთა საერთო რაოდენობა მსოფლიოში 537 მილიონს აღწევს და დიაბეტიან პირთა რიცხვი ყოველწლიურად იზრდება.

შდ იყოფა 3 ძირითად ტიპად: ტიპი 1, ტიპი 2 და გესტაციური დიაბეტი. არსებობს მოდიფიცირებადი და არამოდიფიცირებადი რისკის ფაქტორები, რომლებიც იწვევს არაგადამდები დაავადებების და მათ შორის, დიაბეტის განვითარებას. მოდიფიცირებადი რისკის ფაქტორების აღმოფხვრამ შეიძლება შეაფერხოს ან თავიდან აგვაცილოს ტიპი 2 და გესტაციური შდ. ამავდროულად, ღრესდღეობით შეუძლებელია ტიპი 1 შდ-ის პრევენცია. თუმცა, ის ფაქტი, რომ ტიპი 1 შდ-ის რისკის ფაქტორები ცნობილია, საშუალებას იძლევა, გამოავლინოთ რისკის ქვეშ მყოფი ადამიანები და დაავადების მანიფესტაციის მომენტში არ დავუშვათ ისეთი მძიმე მდგომარეობები, როგორცაა დიაბეტური კეტოაციდოზი და კომა. ფიქსირდება უფრო და უფრო მეტი გარემო და ქცევითი ფაქტორები, რომლებიც ზრდის შდ-ის განვითარების რისკს. ფაქტორების ეს ორი ჯგუფი იწვევს ფიზიოლოგიური პროცესების უარყოფით ცვლილებებს, რაც თავის მხრივ, იწვევს შდ-ის და სხვა არაგადამდები დაავადებების განვითარებას. ინტერვენციებმა, რომლებიც მიმართულია მოდიფიცირებადი რისკის ფაქტორების აღმოფხვრისკენ, შეიძლება შეამციროს ყველა არაგადამდები დაავადების და პირველ რიგში, შდ-ის გავრცელება.

Introduction: What is Diabetes, Diabetes Classification, Prevalence and Incidence.

Diabetes mellitus (DM) is a chronic, metabolic disorder that is characterized by hyperglycemia, that seriously damages all organs and systems of the human body. According to the ADA and WHO classification [1,2] DM is classified into 3 main types – type 1, type 2 and gestational diabetes/GDM (or according to the WHO – hyperglycemia during pregnancy, that includes DM first diagnosed during pregnancy and GDM). Specific types of DM, e.g., monogenic diabetes syndromes (such as neonatal and maturity-onset DM of the young), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced DM (such as glucocorticoid use, in the treatment of HIV, or after organ transplantation) are enrolled in a separate group.

DM is a leading cause of morbidity, disablement and mortality. According to Diabetes Atlas published by International Diabetes Federation (IDF) in 2021 [3], there are 537 million people with diabetes globally, though in 2022 during the EASD Annual Meeting in Stockholm and IDF Congress in Lisbon experts stated that this number could have already reached 1 billion. Total annual global health care spending on DM have increased by US\$ 88 billion. Though DM is found in every population, 80% of all cases are registered in low and middle-income countries [2].

The most common type of diabetes is type 2 DM, its share is 90-95% of all DM cases. In the past 3 decades the prevalence of type 2 DM has risen dramatically and has become a generation younger. Only

5-10% of all diabetes population have type 1 DM, previously known as juvenile diabetes or insulin-dependent diabetes.

Globally 1 200 000 children and adolescents aged 0-20 years have type 1 DM, this number reaches 284 900 – in Europe, and 1 239 – in Georgia. Totally there are 8.4 million of people with type 1 diabetes of all ages in the world.

The prevalence of hyperglycemia among pregnant women is 1–12%, while gestational diabetes (GDM) is the most common metabolic complication during pregnancy and affects about 17% of pregnant women [5]. According to IDF Atlas one in six live births (16.8%) are to women with some form of hyperglycemia in pregnancy [2].

Globally 6.7 million people died due to DM (111 100 - in Europe) in 2021 [2]; 175 000 deaths were registered in type 1 DM, 63-70% of people <25 years died as DM was not diagnosed in time [6].

Diabetes Risk Factors, Traditional vs Emerging

Traditional Risk Factors

Common preventable risk factors underline noncommunicable diseases (NCDs). Risk factors that cause most NCDs, including DM can be modifiable (such as BMI $\geq 25\text{kg/m}^2$ [7], disglycemia, lipid disorders [8], low physical activity, unhealthy diet, smoking [additional triple risk – for mother, fetus and baby in his/her future life] [9], excessive alcohol intake, etc. [10]) and non-modifiable (such as age >45yrs, genetics, ethnicity, family history of DM/GDM, CV episode or GDM in anamnesis, low [risk of type 1 DM for a baby] as well as large [risk of type 2 DM for both a mother and child] weight at birth). Back in 1921 Dr Elliot Joslin (1869-1962) wrote that it was more reasonable to pay greater attention to diabetes prevention than to its treatment, Prevention (or even intervention) should be initiated at the stage of prediabetes, when the disease is not yet manifested, and the earlier we start the better. To have a healthy generation, interventions should be initiated in the perinatal period.

As development of all NCDs and mainly DM in 70% depends on environmental risk factors and only in 30% - on genetic ones, prevention predominantly should be aimed at modification of environmental risk factors.

Type 2 Diabetes

Beside common risk factors, there are risks, specific for each of the main types of DM. In addition to those listed above, such conditions as hypertension [epidemiologic study has shown that prevalence of diabetes among people with arterial hypertension was statistically higher than prevalence of hypertension in those with diabetes] [11,12,13], depression [14], PCO, tuberculosis [15,16] contribute to the development of type 2 DM. Lately such conditions as periodontal disease [17], cancer [18], osteoporosis [19], hyperuricemia, that contributes not only to diabetes but to its chronic complications [20], sleep patterns [20,21], vitamin D deficiency [22] were also adopted as type 2 DM risk factors. Intra-relative marriages or marriages in minority religious populations increase the risk of type 1 DM by 30%. Junk food, light drinks, energizers, juices and unhealthy lifestyle (including time spent at the computers and mobile phones) increase the risk of childhood and adult obesity, that in turn increases the risk of type 2 DM in adult population and in adolescents, aged 11-17 yrs.

Type 1 Diabetes

Unfortunately, there is no cure for type 1 DM today. Factors that may raise the risk for this type may be environmental or genetic. Some of them include: family history, genetic predisposition (candidate

genes), geography (the farther to the north – the higher incidence, and vice versa), age at onset (three peaks are registered – 0-2, 4-7 and 10-14yrs), viruses (Ebstein-Barr, coxsackie, mumps, rubella, Adv62, COVID19 virus, cytomegalovirus), *in utero*, perinatal, or early childhood infections, vitamin D and other vitamins (vitamin E and C deficiency), early introduction of cow's milk as complimentary food and its large amount before the age of 1, gluten introduced before 4 or after 7 months of age, excessive nutrition in utero, never being breastfed, use of toxins and chemical compounds, state of the intestine microbiota, psychological stress, maternal preeclampsia, newborn jaundice and cesarean section [23,24].

Risk for a child to develop type 1 DM depends on who of the family members have the condition: it is 2% if a mother has DM, 6% if a father, 5% if one and 10%-12% if 2 siblings have DM. When both parents have DM the risk for a child to develop the condition is 30–35%, and in monozygotic twins the risk reaches 50% [25,26].

Compared to type 2 DM the onset of type 1 is prompt. Most people who develop type 1 DM do not have a first-degree relative with the disease, and a family does not know anything about its signs and symptoms. As a result, a life-threatening condition – diabetes ketoacidosis, may develop. Thus, education of general public, family doctors and school staff play important role in prevention of serious conditions that may be observed at the onset of type 1 DM.

Hyperglycemia During Pregnancy and Gestational Diabetes Mellitus

Prevalence of hyperglycemia and GDM is increasing dramatically. Hyperglycemia during pregnancy (HDP) may be caused by pre-existing DM, both type 1 and 2 (6.2%), DM first diagnosed during pregnancy, also both type 1 and 2 (7.4%), and the most common form of HDP – GDM (86.4%) [2,5].

Beside risk factors common for both, type 2 and gestational DM, discussed above, there are some factors that are specific only for GDM, such as family history of GDM in first-degree relatives, GDM in previous pregnancies, previous recurrent abortions, previous stillbirth/preterm delivery and cesarean sections, macrosomic baby in anamnesis, advanced gestational age, PCOs, gestational hypertension and dyslipidemia, obesity (high BMI prior pregnancy), excessive weight gain during pregnancy, level of education (the lower the education level, the higher GDM risk), short stature (positive association with GDM), parity.

As for type 2 DM, modifiable risk factors for GDM can and should be reduced or even eliminate.

Emerging Risk Factors

Together with traditional risk factors more and more emerging factors that increase the risk of DM are revealed. Following environmental factors have direct effect on the development of all NCDs, including DM: air, water and soil pollution, high level of various chemicals in the environment (methylmercury, mercury, cadmium, insecticides [DDT]) [26,27], endocrine disruptors that can interact with the hormonal system (bisphenol-A [chemical substance used to manufacture certain plastics/resins], flame retardants, pesticides, phthalates) [28], noise and light pollution (cause circadian rhythm disturbance and sleep disorders, that lead to DM development) [29,30], COVID19 virus [31,32], constant uncontrolled use of antibiotics, especially at an early age, and many others.

Conclusion

DM is a major causal factor for severe health conditions, such as blindness, kidney failure, heart attacks, stroke and lower-limb amputation. There is a sharp increase in all mentioned types of DM, the condition has already taken the form of pandemic. Behavioral and environmental factors together with

physiological ones have direct effect on human organism, thus increasing the risk of the development of all NCDs including DM. Known and emerging risk factors have significant negative impact on human health. Early intervention, elimination of the modifiable risk factors and timely diagnosis may help to achieve a globally agreed target to halt the rise in diabetes by 2025.

References:

1. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes—2024; Vol.47, Suppl. 1
2. Classification of Diabetes Mellitus, WHO, 2019
3. Diabetes Atlas, IDF, 2021
4. Lancet 2023; 402: 203–34
5. Prevalence and risk factors of gestational diabetes in the health region of Lleida: a retrospective observational cohort study; Jour. of Endocrin. Investig.; v. 46, pp 2639–2646, 2023
6. G.A Gregory, T I G Robinson, S E Linklater, et al; Global incidence, prevalence, and mortality of type 1 diabetes in 2021 with projection to 2040: a modelling study; Lancet Diabetes Endocrinol; 2022 Oct;10(10):741-760.; doi: 10.1016/S2213-8587(22)00218-2. Epub 2022 Sep 13
7. Forecasting Obesity and Type 2 Diabetes Incidence and Burden: The ViLA-Obesity Simulation Model. Front. Public Health, 05 April 2022, Sec. Public Health and Nutrition, V. 10 - 2022
8. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021; Lancet 2023; 402: 203–34 Published Online June 22, 2023.
9. Tobacco and diabetes: WHO tobacco knowledge summaries; World Health Organization 2023
10. Atsushi Tanaka, Koichi Node: Emerging roles of sodium–glucose cotransporter 2 inhibitors in cardiology; J. of Cardiology, v. 69, Is. 3, 2017, pp 501-507
11. Cho NH, Kim KM, Choi SH, et al; Diabetes Care. 2015 Jul;38(7)
12. Geiss L.S et al, Am. J. Prev. Med;2002;22:42-8
13. NHANES – 3rd US National Health and Nutrition Examination Survey, 1988-1994
14. Jared G. Maina, Zhanna Balkhiyarova, et al. Bidirectional Mendelian Randomization and Multiphenotype GWAS Show Causality and Shared Pathophysiology Between Depression and Type 2 Diabetes; Diabetes Care 2023;46(9):1707–1714
15. Baghaei et al. Journal of Diabetes & Metabolic Disorders 2013, 12:58
16. Jiménez-Corona ME, et al. Thorax 2013;68:214–220.
17. Salme E Lavigne, Jane L Forrest; An umbrella review of systematic reviews examining the relationship between type 2 diabetes and periodontitis: Position paper from the Canadian Dental Hygienists Association; Can J Dent Hyg. 2021 Feb; 55(1): 57–67.
18. Hwangbo Y, Kang D, Kang M, et al., Incidence of diabetes after cancer development: a Korean National Cohort Study, JAMA Oncol., June, 2018. doi: 10.1001/jamaoncol.2018.1684.
19. Site-Specific Fracture Incidence Rates Among Patients With Type 1 Diabetes, Type 2 Diabetes or Without Diabetes in Denmark (1997–2017), Diabetes Care, 2023. doi:10.2337/dc22-1004
20. Shailendra K Singh, Rina Singh, et al; Uric acid and diabetes mellitus: an update; Postgraduate Medical Journal, 2023 Dec; 99(1178):1220–1225, <https://doi.org/10.1093/postmj/qgad081>
21. Zhilei Sh., Hangfei Ma, et al, Diabetis Care, v. 38, pp 529-537, March, 2015.
22. Harvard Medical School, Analyses of the Nurses' Health Study Data (1976, 1989 and 2010)
23. The Journal of Clinical Endocrinology & Metabolism, 2014
24. <https://www.mayoclinic.org/diseases-conditions/type-1-diabetes/symptoms-causes/syc-20353011>
25. Risk Factors for Type 1 Diabetes; Lars C. Stene, Jill M. Norris, Marian J. Rewers; Diabetes in America; National Library of Medicine, 2023
26. Francesco Chiarelli, Cosimo Giannini, and Marina Primavera; JSPE International Prize Prediction and prevention of type 1 diabetes in children Clin. Pediatr. Endocrinol., 2019; 28(3), 43–57.
27. Endocrine Disruptors, National Institute of Environmental Health Sciences, <https://www.niehs.nih.gov/health/topics/agents/endocrine>

28. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021; *Lancet* 2023; 402: 203–34.
29. 19 July 2023, Parliament, the House of Lords Commission Report
30. According to data from the UK Health Security Agency (UKHSA); EEA 2020 report on Healthy environment, healthy lives: how the environment influences health and well-being in Europe
31. Laura Montefusco, Moufida Ben Nasr, Paolo Fiorina, et al., Acute and long-term disruption of glycometabolic control after SARS-CoV-2 infection; *Nature Metabolism*, v. 3, pp. 774–785, 2021
32. Hanne Løvdal Gulseth, German Tapia, et al, Norwegian Institute of Public Health, Oslo, Norway, EASD-2022, Stockholm, Sweden

RAMAZ KURASHVILI^{1,2}, *ELENA SHELESTOVA*^{1,3}
**THE ROLE OF TRADITIONAL AND EMERGING RISK FACTORS
IN THE DEVELOPMENT OF DIABETES MELLITUS**

¹ National Center for Diabetes Research; ²European University;

³ Georgian National University SEU; Tbilisi, Georgia

SUMMARY

Diabetes mellitus (DM) is a chronic condition characterized by hyperglycemia. Total number of people with DM globally is already 537 million and is on the rise. DM is classified into 3 main types: type 1, type 2 and gestational diabetes. There are modifiable and non-modifiable risk factors that underline NCDs including DM. Elimination of modifiable risk factors may delay or even prevent development of type 2 and gestational DM. Though today it is not possible to prevent type 1 DM. Knowing type 1 DM risk factors we can identify at risk population and prevent severe conditions, diabetes ketoacidosis and coma at the moment of diagnoses. The number of environmental and behavioral factors that elevate the risk of DM is increasing. Those two groups of factors induce negative changes in physiological factors, that in turn cause DM and other NCDs development. Interventions aimed at the reduction of modifiable risk factors may reduce the tide of all NCDs and firstly DM

Keywords: diabetes mellitus, type 1/type 2, gestational, risk factors, development, prevention

