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# THE SIGNIFICANCE OF CENTRAL VISUAL FIELD DEFECTS IN PRIMARY OPEN-ANGLE GLAUCOMA

**Introduction:** In primary open-angle glaucoma (POAG), the focus has traditionally been on peripheral visual field defects. However, over the past 15 years, it has become apparent that the central visual field is affected at an early stage in POAG. The fundamentals and the most important risk factors will be presented.
**Methods:** This study is a literature review. Databases including PubMed, Scopus, Web of Science, and Springer were searched using the terms "central visual field" and "glaucoma" for the period from 2000 to 2025. Duplicates were removed. The selected literature focused on the role of lamina cribrosa, ocular microcirculation, and neurodegeneration in glaucoma.
**Results:** Approximately 50% of retinal ganglion cells (RGCs) are responsible for the central 16° of the visual field alone, and around 40% of these cells are affected in POAG. This leads to abnormalities in the central visual field even in the early stages of POAG. The problem is that the 24-2 or 30-2 visual field program does not adequately detect these central disturbances. The degeneration of RGCs and their nerve fibers is a complex process involving mechanical (intraocular pressure), vascular, and, above all, inflammatory processes.
**Conclusion:** Central RGC loss is not only associated with early central visual field defects, but also leads to color vision defects, contrast sensitivity defects, crowding, and reading difficulties, which significantly impair patients' everyday lives. Therefore, in addition to adjusting intraocular pressure to the individual target pressure range, it is particularly important to have general systemic diseases such as arterial hypertension and diabetes mellitus optimally controlled by an internist and to avoid a nocturnal drop in blood pressure.
**Keywords:** central visual field, lamina cribrosa, glaucoma, neurodegeneration, microcirculation.

## Introduction

Central visual field defects in primary open-angle glaucoma (POAG) are of great clinical significance, but they are generally given too little attention. The aim of this article is therefore to describe this perimetric feature in more detail.

Primary open-angle glaucoma (POAG) is not an isolated optic neuropathy, but rather a systemic neurodegeneration [1,2]. In addition to the glaucoma-typical changes in the optic nerve, including involvement of the entire visual system (lateral geniculate nucleus, optic radiation, visual cortex), there are also generalized cerebral impairments with synaptic connection disorders [3,4] involving both the central autonomic network and the peripheral autonomic nervous system [3,4,5].

The importance of the visual system for humans is reflected in its large involvement in the cerebral cortex. In addition to the primary visual cortex (V1), which accounts for about 15% of the entire cerebral cortex, more than 30 different visual areas have been described to date. In total, about 60% of the cerebral cortex is involved in the perception, interpretation, and response to visual stimuli [6].

Visual impairment in glaucoma is primarily determined by visual field defects. There are various types of classifications, such as the visual classification according to Aulhorn and Karmeyer [7], the classification using the mean defect and the number of defective test locations (Hodapp–Parrish classification) [8], and a classification using the mean defect and the pattern standard deviation (Brusini classification) [9]. These classifications are used to classify perimetric findings according to the severity of functional optic nerve damage, but they do not correspond to individual loss patterns and do not allow the findings to be localized, i.e., whether they originated locally in the optic nerve or in the central nervous system in glaucomatous neurodegeneration.

## Material and methods

This study is an evaluation review. The literature was searched in the databases PubMed, Scopus, Web of Science, and Springer. Duplicate publications have been checked and deleted. The literature search was carried out using the terms "central visual field" and "glaucoma" in the period 2000 to 2025. The selected literature focused on the role of lamina cribrosa, ocular microcirculation, and neurodegeneration in glaucoma.

## Results and discussion

The human optic nerve contains an average of 1.023 million nerve fibers with a wide range of ± 310,000 nerve fibers [10]. There is a retinotopic organization in the prelaminar optic nerve, where neighboring fibers from neighboring retinal areas enter it [10]. Basically, the peripheral retinal areas are located at the outer edge of the optic nerve, while the central parts are located in the center. The axons from the retinal ganglion cells in the macular run via the papillomacular bundle directly to the optic nerve head and are thus located centrally-temporally [10]. The special feature of the macular region is that no axons run over the macula [11]. In the prelaminar section, the retinal nerve fibers (RNF) are unmyelinated, while after the lamina cribrosa they are myelinated by oligodendrocytes [10]. The cellular composition of the lamina cribrosa consists mainly of microglia cells, astrocytes, and alpha-actin-positive lamina cribrosa cells, which are bounded toward the sclera by the Elschnig ring [12]. Its main function is to allow the RNF to pass through the sclera and to equalize the pressure between the prelaminar intraocular pressure (IOP) and the postlaminar cerebrospinal fluid pressure (translaminar pressure difference).

### *Blood supply to the optic nerve*

The optic nerve is supplied with blood via the ophthalmic artery, which branches off from the internal carotid artery. The outer parts of the optic disc and the lamina cribrosa are supplied by the posterior short ciliary arteries via the Zinn–Haller vascular ring, while the central nerve fibers are supplied by branches of the central retinal artery [13]. The special feature of papillary blood supply is that it is autoregulated, i.e., it can maintain a constant flow within certain limits. A distinction is made between metabolic autoregulation, which is based on the current metabolic activity of the retinal ganglion cells (RGC), and pressure-dependent autoregulation [14]. The latter maintains a constant blood flow at the optic nerve head under increased intraocular pressure [15] and intraluminally under both increased and decreased blood pressure [14,16]. The endothelium of the retinal vessels [17] and its interaction with the pericytes [18] play an important role here, as they are regulated by the peripheral autonomic nervous system [19].

### *Central visual field*

In perimetric testing, the central 10° are defined as the central visual field. This primarily examines the macula and fovea. Due to the high importance of this retinal region for visual acuity, contrast, and color vision, 50% of all ganglion cells are located within the central 16° of the visual field, an area that corresponds to only 7.3% of the total surface area of the retina [20]. These findings were confirmed by Zhang [21] using optical coherence tomography (OCT): the average estimated number of RGCs in the macula is 520,678 ± 106,843 cells in healthy eyes, with an average estimated total number of RGCs of 1,042,019 ± 185,243 cells; the estimated number of RGCs in the macula corresponds to approximately 50% of the estimated total number of RGCs. These figures underscore the great importance of the central visual field for the overall evaluation of a perimetric finding. In addition, the central 10 degrees occupy at least 50–60%, and the central 30 degrees of the visual field occupy 83% of the visual cortex [22].

### *POAG and central visual field defects*

Typically, visual field defects in glaucoma are primarily assumed to be peripheral visual field defects as the first signs of damage in the visual field, as it is generally accepted that increased IOP first mechanically impairs the peripheral nerve fibers in the optic nerve head. Compression at the Elschnig ring causes disturbances in the axoplasmic flow of these nerve fibers [23], which ultimately leads to the onset of peripheral visual field defects. This view, which focuses on damage caused by intraocular pressure, has meant that the central visual field is still not routinely assessed in POAG patients. In addition, the standard perimetric examination for glaucoma using the 24-2 or 30-2 visual field with the Humphrey Field Analyzer (Zeiss Meditec AG, Jena) does not take sufficient account of the central area, as there are only 12 test points in the 10° range with the 6° grid in the 24-2/30-2 program. In comparison, the G-1 program in the Octopus (Haag-Streit AG, Koeniz, Switzerland) covers the central visual field better with 17 test points in the 10° range and is considered a good compromise to the special macula program [24].

In addition, in achromatic perimetry, the first scotomas only appear when there is a loss of approximately 30% of retinal ganglion cells [25]. As a result, early visual changes are not detected in time. Motion perimetry methods such as frequency doubling perimetry (Matrix, Zeiss Meditec) or flicker perimetry (Pulsar, Haag-Streit) have proven to be good complementary perimetric methods that can detect visual changes earlier [26,27].

In general, a distinction can be made between POAG-independent and POAG-associated central visual field defects. The first group includes additional pathologies of the macula that are not directly related to POAG, such as age-related macular degeneration, macular epiretinal gliosis, or myopic maculopathy.

On the other hand, POAG itself causes a significant decrease in RGCs, including in the macula. While the average estimated number of RGCs in the macula in healthy eyes was 520,678 ± 106,843 cells, it was already lower in eyes with suspected glaucoma at 410,003 ± 83,887 cells, but in patients with glaucoma it was significantly reduced to 306,010 ± 109,447 cells. Thus, compared to the estimated number of RGCs in the macula, eyes with glaucoma had an average of 41% fewer RGCs in the macula of healthy eyes [21].

These figures clearly demonstrate the significant impact of glaucomatous neurodegeneration on the macular region, which is not solely affected by individually elevated intraocular pressure. This is because the oxidative stress triggered by primary mitochondrialopathy [28,29], which has been significantly detected in both aqueous humor and serum [30], causes retinal and systemic neuroinflammation [31]. This also leads to oxidative stress and neuroinflammation in the optic nerve and lamina cribrosa with activation of microglia, astrocytes, and connective tissue lamina cribrosa cells [12]. In addition to these direct impairments of the RGC and their corresponding nerve fibers, the inflammatory changes in the cellular environment lead to disturbances in the metabolic autoregulation of papillary perfusion and, due to extensive disruption of the central nervous system in POAG [32], to a negative influence on the peripheral autonomic nervous system [33], so that the pressure-dependent autoregulation of papillary perfusion is also disturbed in POAG [34]. In addition, mitochondrial dysfunction itself causes vascular endothelial dysfunction [35], which can further worsen papillary perfusion. In this respect, the degeneration of RGCs and their nerve fibers is a complex process involving mechanical, vascular, and, above all, inflammatory processes [36] that have a direct influence on the development of perimetric disturbances [37,38].

Since 75% of POAG patients have arterial hypertension, 50% have dyslipidemia, and 30% have diabetes mellitus [39], all three of which trigger secondary mitochondriopathy [40,41,42], this leads to a further increase in oxidative stress, neuroinflammation, and small vessel disease. Clinically, these considerations are confirmed by the fact that central visual field defects in POAG occur more frequently in the presence of arterial hypertension or diabetes mellitus [43]. In normal-tension glaucoma, a connection between central visual field defects and migraine, Raynaud's disease, sleep disorders, low blood pressure [44], and nocturnal blood pressure drops 45] has been demonstrated. In advanced glaucoma, the use of antihypertensive therapy is an additional risk factor for central visual field defects [46], which underscores the importance of arterial hypertension. Other risk factors for central visual field defects include optic disc hemorrhages [47,48], reduced choroidal vascular density in the parapapillary β-atrophy zone [49], nasalization of the central retinal vessel trunk [50,51], and reduced vascular density in the foveal avascular zone as well as its enlargement [52]. In the context of biomechanical instability of the lamina cribrosa in POAG [53], a connection with reduced corneal hysteresis and central visual field defects has also been demonstrated [54].

Usually, the nasal step is the earliest visual field defect in POAG patients, followed by paracentral and arcuate-like scotomas, respectively, and the superior hemifield is more often affected than the inferior hemifield [55]. However, central visual field defects occur even in the early stages of glaucoma and are about as common as peripheral visual field defects [56,57,58]. It has also been shown that optic discs with localized notches, known as the focal ischemic type, are significantly more likely to have central visual field defects than optic discs of the senile sclerotic type [59]. Since central visual field defects can progress more rapidly than peripheral scotomas [60], their detection is of great importance, as central visual functions are directly threatened. Temporal papillomacular bundle visual subfield defects were significantly associated with future deterioration in visual acuity in advanced glaucoma [61].

## Conclusion

Central visual field defects in glaucoma are given far too little attention in everyday life, even though approximately 50% of retinal ganglion cells are re-

sponsible for the central 16° of the visual field alone, and 40% of these cells are affected in glaucoma. The early clinical effects of these central RGC losses are color vision disorders, contrast sensitivity disorders, crowding (difficulty recognizing objects when they are close together), and reading difficulties [62,63], which, like color perception disorders [64], can be detected before the onset of scotomas in achromatic threshold perimetry

However, early perimetric changes in the central visual field can be detected with special glaucoma programs, such as the G-1 program, or with macula programs before structural changes are visible in OCT [65], which is also to be expected from the biological sequence of neurodegenerative events [66]. It is clinically important to consider accompanying vascular system diseases in POAG, which have a significant influence on the development of central visual field defects in glaucoma. It is therefore essential to evaluate patients with POAG with a blood count (LDL cholesterol, HbA1c) and a 24-hour blood pressure profile and to adjust their treatment accordingly [67]in order to keep central visual field defects to a minimum. This is because the primary goal of glaucoma therapy is not purely to reduce intraocular pressure numerically, but to preserve visual function [68], which requires a holistic therapeutic approach combining local and systemic therapy.

**References**

1. Chan, J. W., Chan, N. C. Y., & Sadun, A. A. (2021). Glaucoma as neurodegeneration in the brain. *Eye and Brain*, 13, 21–28. https://doi.org/10.2147/EB.S293765

2. Wey, S., Amanullah, S., Spaeth, G. L., Ustaoglu, M., Rahmatnejad, K., & Katz, L. J. (2019). Is primary open-angle glaucoma an ocular manifestation of systemic disease? *Graefe's Archive for Clinical and Experimental Ophthalmology, 257*(4), 665–673. https://doi.org/10.1007/s00417-019-04239-9

. 3. Nuzzi, R., Dallorto, L., & Rolle, T. (2018). Changes of visual pathway and brain connectivity in glaucoma: A systematic review. *Frontiers in Neuroscience, 12*, 363. https://doi.org/10.3389/fnins.2018.00363

4. Sabel, B. A., & Lehnigk, L. (2021). Is mental stress the primary cause of glaucoma? *Klinische Monatsblätter für Augenheilkunde, 238*(2), 132–145. https://doi.org/10.1055/a-1303-8025

5. Sklerov, M., Dayan, E., & Browner, N. (2019). Functional neuroimaging of the central autonomic network: Recent developments and clinical implications. *Clinical Autonomic Research, 29*(6), 555–566. https://doi.org/10.1007/s10286-018-0577-0.

6. Gegenfurtner, K. R., Walter, S., & Braun, D. I. (2002). Visuelle Informationsverarbeitung im Gehirn. In H. D. Huber, B. Lockermann, & M. Scheibel (Eds.), *Bild | Medien | Wissen: Visuelle Kompetenz im Medienzeitalter*. Kopaed Verlag.

7. Aulhorn, E., & Karmeyer, H. (1977). Frequency distribution in early glaucomatous visual field defects. *Documenta Ophthalmologica Proceedings Series, 14*, 75–83.

8. Hodapp, E., Parrish, R. K., II, & Anderson, D. R. (1993). *Clinical decisions in glaucoma*. Mosby.

9. Brusini, P., & Filacorda, S. (2006). Enhanced glaucoma staging system (GSS 2) for classifying functional damage in glaucoma. *Journal of Glaucoma, 15*(1), 40–46. https://doi.org/10.1097/01.ijg.0000195932.48288.97

10. awar, P. R., Booth, J., Neely, A., McIlwaine, G., & Lueck, C. J. (2024). Nerve fibre organisation in the human optic nerve and chiasm: What do we really know? *Eye, 38*(12), 2457–2471. https://doi.org/10.1038/s41433-024-03137-7

11. Airaksinen, P. J., Doro, S., & Veijola, J. (2008). Conformal geometry of the retinal nerve fiber layer. *Proceedings of the National Academy of Sciences of the United States of America, 105*(50), 19690–19695. https://doi.org/10.1073/pnas.0801621105

12 Airaksinen, P. J., Doro, S., & Veijola, J. (2008). Conformal geometry of the retinal nerve fiber layer. *Proceedings of the National Academy of Sciences of the United States of America, 105*(50), 19690–19695. https://doi.org/10.1073/pnas.0801621105

13Mackenzie, P. J., & Cioffi, G. A. (2008). Vascular anatomy of the optic nerve head. *Canadian Journal of Ophthalmology, 43*(3), 308–312. https://doi.org/10.3129/i08-042.

14. Harris, A., Ciulla, T. A., Chung, H. S., & Martin, B. (1998). Regulation of retinal and optic nerve blood flow. *Archives of Ophthalmology, 116*(11), 1491–1495. https://doi.org/10.1001/archopht.116.11.1491

15. Pillunat, L. E., Anderson, D. R., Knighton, R. W., Joos, K. M., & Feuer, W. J. (1997). Autoregulation of human optic nerve head circulation in response to increased intraocular pressure. *Experimental Eye Research, 64*(5), 737–744. https://doi.org/10.1006/exer.1996.0263

16. Venkataraman, S. T., Flanagan, J. G., & Hudson, C. (2010). Vascular reactivity of optic nerve head and retinal blood vessels in glaucoma: A review. *Microcirculation, 17*(7), 568–581. https://doi.org/10.1111/j.1549-8719.2010.00045.

17. Bharadwaj, A. S., Appukuttan, B., Wilmarth, P. A., Pan, Y., Stempel, A. J., Chipps, T. J., Benedetti, E. E., Zamora, D. O., Choi, D., David, L. L., & Smith, J. R. (2013). Role of the retinal vascular endothelial cell in ocular disease. *Progress in Retinal and Eye Research, 32*, 102–180. https://doi.org/10.1016/j.preteyeres.2012.08.004

18. Huang, H. (2020). Pericyte-endothelial interactions in the retinal microvasculature. *International Journal of Molecular Sciences, 21*(19), 7413. https://doi.org/10.3390/ijms21197413

19. Sheng, Y., & Zhu, L. (2018). The crosstalk between autonomic nervous system and blood vessels. *International Journal of Physiology, Pathophysiology and Pharmacology, 10*(1), 17–28.

20. Curcio, C. A., & Allen, K. A. (1990). Topography of ganglion cells in human retina. *Journal of Comparative Neurology, 300*(1), 5–25. https://doi.org/10.1002/cne.903000103

21. Zhang, C., Tatham, A. J., Weinreb, R. N., Zangwill, L. M., Yang, Z., Zhang, J. Z., & Medeiros, F. A. (2014). Relationship between ganglion cell layer thickness and estimated retinal ganglion cell counts in the glaucomatous macula. *Ophthalmology, 121*(12), 2371–2379. https://doi.org/10.1016/j.ophtha.2014.06.047

22. Lindegger, D. J., & Pless, M. (2019). The discovery of visual field representation in the brain. *Journal of Ophthalmology Sciences, 1*(1), 6–12.

23. Dias, M. S., Luo, X., Ribas, V. T., Petrs-Silva, H., & Koch, J. C. (2022). The role of axonal transport in glaucoma. *International Journal of Molecular Sciences, 23*(7), 3935. https://doi.org/10.3390/ijms23073935

24. Roberti, G., Manni, G., Riva, I., Holló, G., Quaranta, L., Agnifili, L., Figus, M., Giammaria, S., Rastelli, D., & Oddone, F. (2017). Detection of central visual field defects in early glaucomatous eyes: Comparison of Humphrey and Octopus perimetry. *PLOS ONE, 12*(10), e0186793. https://doi.org/10.1371/journal.pone.0186793

25. Medeiros, F. A., Lisboa, R., Weinreb, R. N., Liebmann, J. M., Girkin, C., & Zangwill, L. M. (2013). Retinal ganglion cell count estimates associated with early development of visual field defects in glaucoma. *Ophthalmology, 120*(4), 736–744. https://doi.org/10.1016/j.ophtha.2012.09.039

26. Cello, K. E., Nelson-Quigg, J. M., & Johnson, C. A. (2000). Frequency doubling technology perimetry for detection of glaucomatous visual field loss. *American Journal of Ophthalmology, 129*(3), 314–322. https://doi.org/10.1016/S0002-9394(99)00414-6

27Göbel, K., & Erb, C. (2013). Sensitivity and specificity of flicker perimetry with the Pulsar: Comparison with achromatic (white-on-white) perimetry in glaucoma patients. *Der Ophthalmologe, 110*(2), 141–145. https://doi.org/10.1007/s00347-012-2693-x

28u, W. K., Perkins, G. A., Kim, K. Y., Bastola, T., Choi, W. Y., & Choi, S. H. (2023). Glaucomatous optic neuropathy: Mitochondrial dynamics, dysfunction and protection in retinal ganglion cells. *Progress in Retinal and Eye Research, 95*, 101136. https://doi.org/10.1016/j.preteyeres.2023.101136

29. Zhang, Z. Q., Xie, Z., Chen, S. Y., & Zhang, X. (2023). Mitochondrial dysfunction in glaucomatous degeneration. *International Journal of Ophthalmology, 16*(5), 811–823. https://doi.org/10.18240/ijo.2023.05.20

30Benoist d'Azy, C., Pereira, B., Chiambaretta, F., & Dutheil, F. (2016). Oxidative and anti-oxidative stress markers in chronic glaucoma: A systematic review and meta-analysis. *PLOS ONE, 11*(12), e0166915. https://doi.org/10.1371/journal.pone.0166915

31. Tezel, G. (2022). Molecular regulation of neuroinflammation in glaucoma: Current knowledge and the ongoing search for new treatment targets. *Progress in Retinal and Eye Research, 87*, 100998. https://doi.org/10.1016/j.preteyeres.2021.100998

32. abel, B. A., & Lehnigk, L. (2021). Is mental stress the primary cause of glaucoma? *Klinische Monatsblätter für Augenheilkunde, 238*(2), 132–145.

33Liu, B., Zhao, Y., & Zhang, H. (2022). The effect of autonomic nervous system dysfunction on the progression of primary open-angle glaucoma. *International Journal of General Medicine, 15*, 4565–4573. https://doi.org/10.2147/IJGM.S362275

34. Jones, A., Kaplowitz, K., & Saeedi, O. (2014). Autoregulation of optic nerve head blood flow and its role in open-angle glaucoma. *Expert Review of Ophthalmology, 9*, 487–501. https://doi.org/10.1586/17469899.2014.975796

35Prajapat, S. K., Maharana, K. C., & Singh, S. (2024). Mitochondrial dysfunction in the pathogenesis of endothelial dysfunction. *Molecular and Cellular Biochemistry, 479*(8), 1999–2016. https://doi.org/10.1007/s11010-023-04835-8

36Si, Z., Fan, Y., Wang, M., Zhao, J., Zhang, Y., Liu, D., & Zheng, Y. (2025). The role of RGC degeneration in the pathogenesis of glaucoma. *International Journal of Biological Sciences, 21*(1), 211–232. https://doi.org/10.7150/ijbs.103222

37. Aref, A. A., Maleki, S., Tan, O., Huang, D., Varma, R., & Shahidi, M. (2019). Relating glaucomatous visual field loss to retinal oxygen delivery and metabolism. *Acta Ophthalmologica, 97*(7), e968–e972. https://doi.org/10.1111/aos.14120

38Hwang, J. C., Konduru, R., Zhang, X., Tan, O., Francis, B. A., Varma, R., Sehi, M., Greenfield, D. S., Sadda, S. R., & Huang, D. (2012). Relationship among visual field, blood flow, and neural structure measurements in glaucoma. *Investigative Ophthalmology & Visual Science, 53*(6), 3020–3026. https://doi.org/10.1167/iovs.11-8552

39. Manz, K. C., Mocek, A., Höer, A., Simantiri, C., Heuck, A., Eberhardt, A., Mrosowsky, T., Zander, S., Fritz, B., Schuster, A. K., & Erb, C. (2024). Epidemiology and treatment of patients with primary open-angle glaucoma in Germany: A health claims data analysis. *Journal of Glaucoma, 33*(8), 549–558. https://doi.org/10.1097/IJG.0000000000002420

40. Touyz, R. M., Rios, F. J., Alves-Lopes, R., Neves, K. B., Camargo, L. L., & Montezano, A. C. (2020). Oxidative stress: A unifying paradigm in hypertension. *Canadian Journal of Cardiology, 36*(5), 659–670. https://doi.org/10.1016/j.cjca.2020.02.081.

41Miller, Y. I., & Shyy, J. Y. (2017). Context-dependent role of oxidized lipids and lipoproteins in inflammation. *Trends in Endocrinology & Metabolism, 28*(2), 143–152. https://doi.org/10.1016/j.tem.2016.11.002

42Manojlovic, M., Zafirovic, S., Tomic Naglic, D., Stokic, E., Rizzo, M., Suri, J. S., & Isenovic, E. (2025). Mitochondrial dysfunction, reactive oxygen species, and diabetes mellitus – A triangular relationship: A review. *Biomolecules and Biomedicine*. https://doi.org/10.17305/bb.2025.13145

43. Kim, J. M., Kyung, H., Shim, S. H., Azarbod, P., & Caprioli, J. (2015). Location of initial visual field defects in glaucoma and their modes of deterioration. *Investigative Ophthalmology & Visual Science, 56*(13), 7956–7962. https://doi.org/10.1167/iovs.15-17297

44Kang, J. W., Park, B., & Cho, B. J. (2015). Comparison of risk factors for initial central scotoma versus initial peripheral scotoma in normal-tension glaucoma. *Korean Journal of Ophthalmology, 29*(2), 102–108. https://doi.org/10.3341/kjo.2015.29.2.102

45. Im, S. I., Cha, C., Lee, S., & Lee, S. (2025). Nocturnal diastolic hypotension is associated with central visual field defect in early and moderate normal-tension glaucoma. *Graefe's Archive for Clinical and Experimental Ophthalmology, 263*(8), 2307–2314. https://doi.org/10.1007/s00417-025-06813-w

46Sugisaki, K., Inoue, T., Yoshikawa, K., Kanamori, A., Yamazaki, Y., Ishikawa, S., Uchida, K., Iwase, A., Araie, M., & Advanced Glaucoma Study Members in Japan Glaucoma Society. (2022). Factors threatening central visual function of patients with advanced glaucoma: A prospective longitudinal observational study. *Ophthalmology, 129*(5), 488–497. https://doi.org/10.1016/j.ophtha.2021.11.025

47. David, R. C. C., Moghimi, S., Do, J. L., Hou, H., Proudfoot, J., Zangwill, L. M., Kamalipour, A., Nishida, T., De Moraes, C. G., Girkin, C. A., Liebmann, J. M., & Weinreb, R. N. (2021). Characteristics of central visual field progression in eyes with optic disc hemorrhage. *American Journal of Ophthalmology, 231*, 109–119. https://doi.org/10.1016/j.ajo.2021.05.026

48Shukla, A. G., Sirinek, P. E., De Moraes, C. G., Blumberg, D. M., Cioffi, G. A., Skaat, A., Girkin, C. A., Weinreb, R. N., Zangwill, L. M., Hood, D. C., & Liebmann, J. M. (2020). Disc hemorrhages are associated with the presence and progression of glaucomatous central visual field defects. *Journal of Glaucoma, 29*(6), 429–434. https://doi.org/10.1097/IJG.0000000000001487

49. Kim, E. K., Park, H. L., Hong, K. E., Shin, D. Y., & Park, C. K. (2021). Investigation of progression pattern and associated risk factors in glaucoma patients with initial paracentral scotomas using Humphrey 10-2. *Scientific Reports, 11*(1), 18609. https://doi.org/10.1038/s41598-021-97446-6

50Shon, K., Jo, Y. H., Shin, J. W., Kwon, J., Jeong, D., & Kook, M. S. (2020). Nasalization of central retinal vessel trunk predicts rapid progression of central visual field in open-angle glaucoma. *Scientific Reports, 10*(1), 3789. https://doi.org/10.1038/s41598-020-60355-1

51. Bak, E., Kim, M., Kim, S. H., & Lee, K. M. (2024). Optic nerve head factors associated with initial central visual field defect in primary open-angle glaucoma. *Scientific Reports, 14*(1), 8000. https://doi.org/10.1038/s41598-024-58749-6

52. Yoon, J., Kim, K. E., Lee, A., Song, W. K., & Kook, M. S. (2023). Foveal avascular zone vessel density is associated with visual field progression in early-stage glaucoma eyes with central visual field damage. *Scientific Reports, 13*(1), 18285. https://doi.org/10.1038/s41598-023-45541-1

53. Ahmad, S. S. (2023). The mechanical theory of glaucoma in terms of prelaminar, laminar, and postlaminar factors. *Taiwan Journal of Ophthalmology, 14*(3), 376–386. https://doi.org/10.4103/tjo.TJO-D-23-00103

54. Kamalipour, A., Moghimi, S., Eslani, M., Nishida, T., Mohammadzadeh, V., Micheletti, E., Girkin, C. A., Fazio, M. A., Liebmann, J. M., Zangwill, L. M., & Weinreb, R. N. (2022). A prospective longitudinal study to investigate corneal hysteresis as a risk factor of central visual field progression in glaucoma. *American Journal of Ophthalmology, 240*, 159–169. https://doi.org/10.1016/j.ajo.2022.02.025

55. Vandersnickt, M. F., van Eijgen, J., Lemmens, S., Stalmans, I., Pinto, L. A., & Vandewalle, E. M. (2024). Visual field patterns in glaucoma: A systematic review. *Saudi Journal of Ophthalmology, 38*(4), 306–315. https://doi.org/10.4103/sjopt.sjopt_143_24

56Schiefer, U., Papageorgiou, E., Sample, P. A., Pascual, J. P., Selig, B., Krapp, E., & Paetzold, J. (2010). Spatial pattern of glaucomatous visual field loss obtained with regionally condensed stimulus arrangements. *Investigative Ophthalmology & Visual Science, 51*(11), 5685–5689. https://doi.org/10.1167/iovs.09-5067

57Hood, D. C., Raza, A. S., de Moraes, C. G., Odel, J. G., Greenstein, V. C., Liebmann, J. M., & Ritch, R. (2011). Initial arcuate defects within the central 10 degrees in glaucoma. *Investigative Ophthalmology & Visual Science, 52*(2), 940–946. https://doi.org/10.1167/iovs.10-5803

58. Traynis, I., De Moraes, C. G., Raza, A. S., Liebmann, J. M., Ritch, R., & Hood, D. C. (2014). Prevalence and nature of early glaucomatous defects in the central 10° of the visual field. *JAMA Ophthalmology, 132*(3), 291–297. https://doi.org/10.1001/jamaophthalmol.2013.7656

59. Ekici, E., Moghimi, S., Hou, H., Proudfoot, J., Zangwill, L. M., Do, J. L., Oh, W. H., Kamalipour, A., Liebmann, J. M., De Moraes, C. G., Girkin, C. A., El-Nimri, N., & Weinreb, R. N. (2021). Central visual field defects in patients with distinct glaucomatous optic disc phenotypes. *American Journal of Ophthalmology, 223*, 229–240. https://doi.org/10.1016/j.ajo.2020.10.015

60. Park, S. C., Kung, Y., Su, D., Simonson, J. L., Furlanetto, R. L., Liebmann, J. M., & Ritch, R. (2013). Parafoveal scotoma progression in glaucoma: Humphrey 10-2 versus 24-2 visual field analysis. *Ophthalmology, 120*(8), 1546–1550. https://doi.org/10.1016/j.ophtha.2013.01.045

61Asaoka, R., Sugisaki, K., Inoue, T., Yoshikawa, K., Kanamori, A., Yamazaki, Y., Ishikawa, S., Uchida, K., Iwase, A., Araie, M., & Advanced Glaucoma Study Members in Japan Glaucoma Society. (2023). Identifying central 10° visual subfield associated with future worsening of visual acuity in eyes with advanced glaucoma. *British Journal of Ophthalmology, 108*(1), 71–77. https://doi.org/10.1136/bjo-2022-321481

62Kwon, M. (2024). Impact of glaucomatous ganglion cell damage on central visual function. *Annual Review of Vision Science, 10*(1), 425–453. https://doi.org/10.1146/annurev-vision-110223-123044

63. Pacheco-Cutillas, M., Edgar, D. F., & Sahraie, A. (1999). Acquired colour vision defects in glaucoma: their detection and clinical significance. *British Journal of Ophthalmology, 83*(12), 1396–1402. https://doi.org/10.1136/bjo.83.12.1396

64. Drance, S. M., Lakowski, R., Schulzer, M., & Douglas, G. R. (1981). Acquired color vision changes in glaucoma: Use of 100-hue test and Pickford anomaloscope as predictors of glaucomatous field change. *Archives of Ophthalmology, 99*(5), 829–831. https://doi.org/10.1001/archopht.1981.03930010829007

65. Hood, D. C. (2019). Does retinal ganglion cell loss precede visual field loss in glaucoma? *Journal of Glaucoma, 28*(11), 945–951. https://doi.org/10.1097/IJG.0000000000001380

66. Porciatti, V., & Ventura, L. M. (2012). Retinal ganglion cell functional plasticity and optic neuropathy: A comprehensive model. *Journal of Neuro-Ophthalmology, 32*(4), 354–358. https://doi.org/10.1097/WNO.0b013e3182745600

67. Hacke, C., Erb, C., & Weisser, B. (2018). Risikofaktoren und Zielwerte in der kardiovaskulären Primär- und Sekundärprävention: Bedeutung für das Glaukom [Risk factors and therapeutic goals for primary and secondary cardiovascular prevention: Significance for the glaucoma patient]. *Klinische Monatsblätter für Augenheilkunde, 235*(2), 151–156. https://doi.org/10.1055/s-0044-101260

68. Montesano, G., Garway-Heath, D. F., & Gazzard, G. (2025). Disease progression, not intraocular pressure, should guide escalation of treatment in glaucoma. *Ophthalmology Glaucoma, 8*(5), 427–430. https://doi.org/10.1016/j.ogla.2025.04.005

*The significance of central visual field defects in primary open-angle glaucoma*

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# ASSOCIATION OF ADVANCING MATERNAL AGE WITH INCREASED SEVERITY OF GESTATIONAL DIABETES MELLITUS (GDM)

**Introduction:** Advanced maternal age parallels the rising prevalence of Gestational Diabetes Mellitus (GDM). Advanced maternal age (AMA ≥35 years) is a known risk factor for GDM, but its specific association with the severity of the condition at diagnosis warrants further investigation.
**Objective:** This study aimed to investigate the association between advancing maternal age and the severity of GDM at the time of diagnosis.
**Methods:** Our study was a hospital-based, retrospective observational study conducted at the Endocrine Clinic of Government Medical College, Baramulla. A total of 85 pregnant women diagnosed with GDM were included and divided into three age groups: < 30 years (n = 16), 30-34 years (n = 44), and ≥35 years (n = 25). Data on sociodemographics, obstetric history, gestational age at diagnosis.
**Results**: In our study, mothers ≥35 years were diagnosed with GDM significantly earlier (mean gestational age: 25.8 weeks) compared to the youngest group (30.6 weeks). They also exhibited significantly higher 1-hour OGTT values (201.7 mg/dL vs. 187.6 mg/dL, p = 0.007) and a trend towards higher HbA1c. The ratio of women with abnormal glycemic values across parameters (fasting, 1-hour, 2-hour OGTT, HbA1c) increased with maternal age. Multivariate analysis confirmed that each one-year increase in maternal age was an independent predictor of an earlier diagnosis and a higher 1-hour OGTT.
**Conclusion:** Increased maternal age is significantly associated with increased severity of GDM at diagnosis, manifesting as an earlier gestational age at detection and more pronounced post-challenge hyperglycemia. These findings highlight the need for vigilant screening and prompt management strategies for pregnant women with advanced age.
**Keywords:** GDM, AMA, OGTT, Multivariate analysis, Early Diagnosis.

## Introduction

Advanced maternal age is characterised by anage ofa female aged 35 years or more at the time of a full-term birth [1]. Gestational diabetes is glucose intolerance resulting in a hyperglycemic state of variable severity with onset during pregnancy.Gestational diabetes mellitus (GDM) poses a significant challenge to public health, with its increasing prevalence in parallelwiththe trend of increasing maternal age [2]. A hyperglycemic condition first recognized during pregnancy is associated with a myriad of short- and long-term consequences for both the mother and neonate [3]. Subsequently, the proportion of pregnant women with advanced maternal age (AMA) (≥35 years) has been growing around the globe, and a demographic shift is being observed in both developed countries and developing countries [4]. GDM pregnancy outcomes may vary by maternal age. One of the studies of 8844 singleton pregnancies highlighted that GDM increased the risk of preterm births and macrosomia among women aged < 35 years [5]. Lack of international consensus at present for the diagnosis of GDM highlights its complex historical birth; higher maternal age is an independent risk factor for GDM [6]. It has been seen that early onset of early onset of preclampsia and the risk of placenta praevia were higher in women aged 40-44 years [7]. Women of advanced maternal age have a higher incidence of medical comorbidities compared to women of < 30 years [8]. The mechanism of the association between maternal age and GDM has not been fully elucidated or understood to date. Insulin resistance, intense levels of circulating adipokines and inflammatory mediators,as well as oxidative impact, may explain this phenomenon [9]

***Aim of the study:***

The aim of our study was to investigate the association between advancing maternal age and the severity of Gestational Diabetes Mellitus (GDM) at the time of diagnosis.

***Objectives of the study:***

Our study will be guided by under objectives:

Compare markers of GDM severity like gestational age at diagnosis, Oral Glucose Fasting 1-hour, 2-hour, and initial HbA1c levels among different maternal age groups.

Determine was maternal age an independent predictor of requiring pharmacological therapyfor GDM management.

**Methodology**

1. Study Design

Our study was a hospital-based, retrospective observational study, conducted to investigate the association between advancing maternal age and the severity of Gestational Diabetes Mellitus (GDM) at diagnosis.The study population consisted of all pregnant women diagnosed with GDM who attended the endocrine clinic at GMC Baramulla during the specified study period.The consecutive convenience-based sampling method was used for the study.The study was conducted in the Endocrine Clinic of the Department of General Medicine, Government Medical College (GMC), Baramulla. Data was collected from patients who attended the specialized endocrine clinic, which operates every Wednesday. Thestudy was conducted from Insert Start Date1st January 2025 to 10$^{th}$July 2025.Ethical approval was obtained from the Institutional Ethics Committee (IEC) of the Government Medical College. Being a retrospective study that involved the analysis of existing anonymized patient data, the requirement for individual informed consent was waived by the ethics committee. All data was handled with strict confidentiality, and patient identifiers were coded prior to analysis to ensure privacy.The collected data, entered into a Microsoft Excel spreadsheet,was analyzed using statistical software IBPM SPSS version 24.0.Mean, standard deviation, frequency, percentage) were used to summarize the data. The groups were stratified into maternal age groups.A **p-**value of $< 0.05$ was considered statistically significant for all tests.Comparison of continuous variables across age groups was done using Analysis of Variance (ANOVA), and Multivariable logistic regression was used to determineif maternal age was an independent predictor for insulin therapy.

**Data Collection**

A structured Excel sheet form wasused to collect information from the patient data stored in the department in the form of electronic and physical medical records.Under data points were systematically extracted:

Sociodemographic and Obstetric Profile: Maternal age, residential address, occupation, gravida, parity.

GDM Diagnosis Details: Gestational Age (GA) at diagnosis, OGTT values (Fasting, 1-hour, 2-hour), and initial HbA1c level.

Treatment Modality: The initial treatment plan was recorded and categorized as 'Diet & Lifestyle Modification' or 'Pharmacological Therapy (Insulin)'.

***Inclusion Criteria:***

All Pregnant women diagnosed with Gestational Diabetes Mellitus (GDM) who are already on follow-up of the endocrine clinic.

All pregnant women who attended their first antenatal care visit and were diagnosed with GDM at the study facility.

Patients having a singleton pregnancy.

Patients having complete clinical records containing data on age, OGTT values, HbA1c at diagnosis, and subsequent GDM management.

***Exclusion Criteria:***

Patients with a pre-existing diagnosis of diabetes mellitus (Type 1 or Type 2) diagnosed prior to the index pregnancy.

Patients with multiple gestations.

Patients with major fetal congenital anomalies.

Patients having incomplete medical records regarding the key study variable.

**Results**

Table 1 indicates of 32.1 years and was categorized into three groups: under 30 years (n=16, 18.8%), 30-34 years (n=44, 51.8%), and 35 years or older (n=25, 29.4%). Women in the oldest group (≥35 years) have a higher number of pregnancies, with 60.0% (n=15) having been pregnant three or more times. In contrast, there were 45.4% (n=20) in the 30-34 year group and 43.7% (n=7) in the under-30 group. The proportion of multiparous women was consistently high and remarkably similar across all age groups. It ranged from 77.3% (n=34) in the 30-34 year group to 80.0% (n=20) in the ≥35 year group. The majority of participants across all age groups were unemployed, predominantly listed

as "Housewives." The proportion of unemployed women was 81.3% (n=13) in the <30 group, 74.0% (n=33) in the 30-34 group, and 72.0% (n=18) in the ≥35 group. The study population was predominantly from rural areas, which was consistent across all strata, with the proportion of rural residents being 81.3% (n=13), 79.5% (n=35), and 76.0% (n=19) for the <30, 30-34, and ≥35 age groups

**Table 1**
*Baseline Characteristics of the Study Population Stratified by Maternal Age*

| Maternal age in years | Total no. | Maternal age<30 years (N=16) | Maternal age 30-34 years (N=44) | Maternal age ≥35 years (N=25) |
|---|---|---|---|---|
| Mean±S.D | 32.1±3.7 | 27.1±1.8 | 32.0±1.4 | 36.6±1.9 |
| Range | 20-42 | 20-29 | 30-34 | 35-42 |
| Gravida | | | | |
| 1 | 17(20.0%) | 4(25.0%) | 9(20.5%) | 4(16.0%) |
| 2 | 26(30.6%) | 5(31.5%) | 15(34.1%) | 6(24.0%) |
| ≥3 | 42(49.4%) | 7(43.7%) | 20(45.4%) | 15(60.0%) |
| Parity | | | | |
| Nulliparous | 19(22.4%) | 4(25.0%) | 10(22.7%) | 5(20%) |
| Multipara | 66(77.6%) | 12(75.05%) | 34(77.3%) | 20(80%) |
| Occupation | | | | |
| Unemployed | 64(75.3%) | 13(81.3%) | 33(74.0%) | 18 (72.0%) |
| Employed | 21(24.7%) | 3(18.7%) | 11(25.0%) | 7(28.05%) |
| Residence | | | | |
| Rural | 67(78.8%) | 13(81.3%) | 35(79.5%) | 19(76.0%) |
| Urban | 18(21.2%) | 8(18.7%0 | 9(20.5%) | 6(24.0%) |

**Table 2**
*GDM Severity at Diagnosis Across Maternal Age Groups*

| Severity marker | Total Number (n=85) | Maternal age <30 years (N=16) | Maternal age 30-34 years (N=44) | Maternal age ≥35 years (N=25) |
|---|---|---|---|---|
| Gestational age at diagnosis in weeks | | | | |
| Mean ±S.D | 27.5 ± 7.4 | 30.6 ± 8.5 | 27.6±7.1 | 25.8 ± 6.8 |
| Median | 28 | 29 | 28 | 27 |
| OGTT after 1 Hour in Mg/dl | | | | |
| Mean ± SD | 194.5 ± 33.4 | 187.6 ± 37.9 | 192.3 ± 31.5 | 201.7 ± 33.7 |
| Median | 190.0 | 189.5 | 187.5 | 199.0 |
| OGTT After 2 hours in Mg/dL | | | | |
| Mean ± SD | 158.0 ± 33.8 | 155.6 ± 33.8 | 156.6 ± 34.0 | 161.2 ± 34.8 |
| Median | 154.0 | 150.5 | 151.5 | 159.0 |
| HbA1c on detection | | | | |
| Mean | 5.51 ± 0.51 | 5.41 ± 0.49 | 5.54 ± 0.53 | 5.58 ± 0.47 |
| Median | 5.60 | 5.45 | 5.60 | 5.60 |

Table 2 indicates that GDM was diagnosed earliest in the oldest mothers (≥35 years), at a mean of 25.8 weeks, pointing to an earlier onset or detection with advanced age,youngest group (<30 years) was diagnosed latest, at 30.6 weeks, indicating a potentially later presentation of the condition, fasting blood glucose levels at diagnosis were similar across all age groups, showing no strong correlation

with maternal age,1-hour post-glucose challenge values were highest in the ≥35 years group (201.7 mg/dL), indicating poorer initial glycemic control,2-hour post-glucose levels also followed this trend, being highest in the oldest age group (161.2 mg/dL), highest median values for both 1-hour (199.0 mg/dL) and 2-hour (159.0 mg/dL) OGTT were in the ≥35 years of age group, initial HbA1c levels were also highest in the oldest group (mean 5.58%), differences were clinically modest,mothers aged 35 and above consistently presented with more severe glycemic disturbances.

**Table 3**
*Abnormal GlycemicPattern amongMaternal Age Groups*

| Glycemic parameter | Limit for abnormality | Total no. | Maternal age <years (n=16) | Maternal Age(30-34 years)n=44 | Maternal Age >35 years(n=25) |
|---|---|---|---|---|---|
| BGF | >95mg/dl | 52(61.2%) | 9 (56.3%) | 27(61.4%) | 16(64%) |
| BG after I Hour | >180mg/dl | 65(76.5%) | 10 (62.5%) | 34(77.3%) | 21( 84%) |
| BG after 2 hours. | >153mg/dl | 52(61.2%) | 8 (50%) | 27(61.4%) | 17(68%) |
| Raised Hba1c | ≥5.7mg/dl | 32(37.6% | 32 (37.6%) | 17(38.65) | 11(44%) |

Table 3 indicates that Abnormality (>95 mg/dl) in fasting blood glucose was common overall (61.2%) and showed a slight increase with age, being highest in the ≥35 years group (64%). Frequently, abnormal parameters after 1 hour overall were in (76.5%), and (≥35 years) had the highest proportion (84%) of women with an abnormal 1-hour value. In the 2-Hour Post-Glucose, 1.2% of women had abnormal values (>153 mg/dl), with the rate rising from 50% in the youngest to 68% in the oldest group. Raised HbA1c was the least common abnormality (37.6%), prevalence of which increased with maternal age, peaking at 44% in the ≥35 years group.The youngest group (<30 years) generally had the lowest rates of abnormality across all parameters.

**Table 4**
*Univariate and multivariable linear regression analysis of factors linked to GDM severity*

| Predicting Variable | P -value Gestational Age in (weeks) at time of diagnosis | p-value OGTTafter 1-Hour Value in mg/dl | p-value Initial HbA1c (%) |
|---|---|---|---|
| Univariate analysis<br>Maternal Age (per 1-year ) | p=0.002 | p=0.006 | p=0.051 |
| Gravida (per 1 pregnancy ) | p=0.516 | p=0.512 | p=0.482 |
| Parity (Multiparous vs. Nulliparous) | p=0.512 | p=0.610 | p=0.505 |
| Occupation (Employed vs. unemployed ) | p=0.439 | p=0.357 | p=0.612 |
| Address (Urban vs. Rural) | p=0.512 | p=0.512 | p=0.806 |
| Multivariable Analysis | | | |
| Maternal Age per 1-year | p=0.004 | p=0.007 | p=0.067 |
| Gravida per 1 pregnancy | p=0.587 | p=0.411 | p=0.551 |
| Parity (Multiparous vs. Nulliparous) | p=0.512 | p=0.610 | p=0.505 |

Table 4 indicates that advancing maternal age had a statistically significant association with all three markers of GDM severity. Each one-year increase in maternal age was associated with a significantly earlier gestational age at diagnosis (p=0.002) and a higher 1-hour OGTT value (p=0.006). A trend was seen for initial HbA1c, marginally non-significant (p=0.051). Gravida, parity, occupation, and addressshowed no significant association with GDM severity markers in the univariate analysis (all p-values > 0.05). Multivariable analysis, which adjusted for the effects of gravida and parity, confirmed that maternal age remained an independent and significant predictor for two key severity markers. Each one-year increase in age was independently associated with significantly earlier gestational age at diagnosis (p=0.004), significantly higher 1-hour OGTT value (p=0.007). Association between maternal age and initial HbA1c was attenuated in the multivariable model and was no longer statistically significant (p=0.067). Gravida and parity continued to show no significant association with any of the severity markers in the adjusted model.

**Review**

Our study focused on the determinants of the rural population. The mean age of participants in our study was 32.1±3.7, which was inline with the study [10]. The obstetric history of our participants is notable for a high rate of multiparity, with 77.6% of women being multiparous and 49.4% having a gravidity of three or more. This trend was particularly pronounced in the advanced maternal age group (≥35 years), where 60% had a gravidity of ≥3. Such findings correspond to the concept of "metabolic memory," repeated pregnancies stress B-cells, and may predispose women to glucose intolerance in subsequent gestations [11]. The Majority of women in our study were unemployed (predominantly housewives) and resided in rural areas (78.8%), and appeared in contrast to the study by Corsi et al [12], this discrepancy can be due to effective and successful implementation of antenatal screening programs by national rural health mission in rural healthcare settings, effectively finding cases that might otherwise go undiagnosed. In India's rural areas, which are undergoing rapid economic and nutritional transitions, the burden of non-communicable diseases like diabetes is expected to affect lower socioeconomic groups increasingly. Our study had multiparity across all age groups, which was in contrast to a study by Dia et al [13] that stated that multiparity wasa protective factor; likely reasons could be a smaller sample size, single-centre study,maternal age, pre-pregnancy BMI, and ethnicity.The high proportion of unemployed women as 'Housewives' in our Gestational Diabetes Mellitus (GDM) cohort is consistent with the demographic profile of the study [14]. The majority of the sample population resided in rural areas,because the study was conducted in the rural tertiary care setting [15]. The mean age in our study participants at the time of diagnosis of GDM was 27.5 years, which corresponded to a study by [16]. Our study noted a progressive increase in mean 1-hour OGTT glucose values with increasing maternal age and the highest values are in women with advanced age, indicating greater post-prandial glucose intolerance and is consistent with the physiological decrease in insulin sensitivity with age corresponding to a literature by Hubert et al [17]. Our study observed 2-hour OGTT glucose showed mild upward trend among women aged ≥35 years, pointing to slightly higher degree of post-load glucose intolerance, aligning with existing evidence [18]. in which Xiang et al. documented that high gravidas exhibit significantly higher 1-hour and 2-hour glucose pointing towards the fact that diminished β-cell compensatory mechanism with advancing age.Our study had a modest increase in HbA1c level with increased maternal age, measurements of which remained within the non-diabetic range. Such a subtle rise is consistent with the range of mild dysglycemiaobserved at the time of GDM diagnosis, causing metabolic disturbance rather than apparent chronic hyperglycemia. Slightly higher HbA1c levels seen among women in advanced age may indicate a longer duration of subclinical insulin resistance prior to diagnosis, consistent with the literature [19]. This study showed that abnormal fasting glucose (BGF >95 mg/dL) was observed in 61.2% of study participants, with increase across age groups, rising from 56.3% in women <30 years to 64% in those ≥35 years, reflects the well-established association between advancing maternal age and impaired fasting glucose levels during pregnancy [20]. Majority of participants had abnormal 1-hour post-challenge glucose (>180 mg/dL), with the highest percentage occurring in the ≥35-year groupsupporting the fact that postprandial glucose dysregulation enhances with age due to declining β-cell reserve[21]. Our study had elevated HbA1c (≥5.7%) in 37.6% of participants overall, with the majority among mothers ≥35 years was in line with the study [22]. where elevations in HbA1c in early pregnancy have been linked with higher risk for GDM and adverse outcomes of pregnancy , especially in older mothers who may en-

ter pregnancy with pre-existing metabolic risks.The progressive rise of abnormal HbA1c level across age categories in our study is therefore consistent with the natural trajectory of age-related blood sugar dysregulation. In our study, maternal age was found to be a significant independent predictor of multiple glycemic parameters in both univariate and multivariable analyses. Higher maternal age was significantly associated with earlier gestational age at diagnosis ($p = 0.002$ univariate; $p = 0.004$ multivariable), higher 1-hour OGTT glucose values ($p = 0.006$ univariate; $p = 0.007$ multivariable), and showed a borderline association with higher HbA1c values ($p = 0.051$ univariate; $p = 0.067$ multivariable) These results were in line with systematic review and meta analysis by yueyi et al[23].

## Conclusion

Our study provides strong evidence that advancing maternal age is significantly associated with increased severity of Gestational Diabetes Mellitus (GDM) at the time of diagnosis. Findingsof our study observed that older mothers (≥35 years) were diagnosed with GDM at an earlier gestational age and showed significantly higher 1-hour post-glucose challenge levels compared to their younger opponents. Continuing trend of increasing abnormality across different glycemicparameters like fasting glucose, 1-hour and 2-hour OGTT values, and HbA1cwas observed with advancing maternal age. Multivariable analysis pointed out that maternal age is an independent predictor for an earlier diagnosis and higher 1-hour OGTT values. This underscores the role of advancing age as a criticalrisk factor for more severe glycemic disturbances in GDM, reflecting the combined impact of age-related declines in β-cell function and insulin sensitivity.

## Gratitude / conflict of interest

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### Refrences

1.F. Cunningham, G., & Leveno, K. J. (1995). Childbearing among older women — The message is cautiously optimistic. *New England Journal of Medicine, 333*, 1002–1004. https://doi.org/10.1056/NEJM199510123331511

2Baz, B., Riveline, J.-P., & Gautier, J.-F. (2016). Endocrinology of pregnancy: Gestational diabetes mellitus: Definition, aetiological and clinical aspects. *European Journal of Endocrinology, 174*(2). https://doi.org/10.1530/EJE-15-0378

3. Li, J., Yan, J., Ma, L., Huang, Y., Zhu, M., & Jiang, W. (2023). Effect of gestational diabetes mellitus on pregnancy outcomes among younger and older women and its additive interaction with advanced maternal age. *Frontiers in Endocrinology, 14*, 1158969. https://doi.org/10.3389/fendo.2023.1158969

4. ao, C., Sun, X., Lu, L., Liu, F., & Yuan, J. (2019). Prevalence of gestational diabetes mellitus in mainland China: A systematic review and meta-analysis. *Journal of Diabetes Investigation, 10*, 154–162. https://doi.org/10.1111/jdi.12854

5. Wang, X., Zhang, X., Zhou, M., Juan, J., & Wang, X. (2021). Association of gestational diabetes mellitus with adverse pregnancy outcomes and its interaction with maternal age in Chinese urban women. *Journal of Diabetes Research, 2021*, 5516937. https://doi.org/10.1155/2021/5516937

6. Li, Y., Ren, X., He, L., Li, J., Zhang, S., & Chen, W. (2020). Maternal age and the risk of gestational diabetes mellitus: A systematic review and meta-analysis of over 120 million participants. *Diabetes Research and Clinical Practice*. https://doi.org/10.1016/j.diabres.2020

7. Marozio, L., Picardo, E., Filippini, C., Mainolfi, E., Berchialla, P., Cavallo, F., Tancredi, A., & Benedetto, C. (2019). Maternal age over 40 years and pregnancy outcome: A hospital-based survey. *Journal of Maternal-Fetal & Neonatal Medicine, 32*(10), 1602–1608. https://doi.org/10.1080/14767058.2017.1410793

8Claramonte Nieto, M., Meler Barrabes, E., Garcia Martínez, S., Gutiérrez Prat, M., & Serra Zantop, B. (2019). Impact of aging on obstetric outcomes: Defining advanced maternal age in Barcelona. *BMC Pregnancy and Childbirth, 19*(1), 342. https://doi.org/10.1186/s12884-019-2415-3

9. hin, D., & Song, W. O. (2015). Prepregnancy body mass index is an independent risk factor for gestational hypertension, gestational diabetes, preterm labor, and small- and large-for-gestational-age infants. *Journal of Maternal-Fetal & Neonatal Medicine, 28*(14), 1679–1686. https://doi.org/10.3109/14767058.2014.964675

10. Swaminathan, G., Swaminathan, A., & Corsi, D. J. (2020). Prevalence of gestational diabetes in India by individual socioeconomic, demographic, and clinical factors. *JAMA Network Open, 3*(11), e2025074. https://doi.org/10.1001/jamanetworkopen.2020.25074

11. Magon, N., & Seshiah, V. (2011). Gestational diabetes mellitus: Non-insulin management. *Indian Journal of Endocrinology and Metabolism, 15*(4), 284–293. https://doi.org/10.4103/2230-8210.85580

12. Corsi, D. J., & Subramanian, S. V. (2012). Association between socioeconomic status and self-reported diabetes in India: A cross-sectional multilevel analysis. *BMJ Open, 2*(4), e000895. https://doi.org/10.1136/bmjopen-2012-000895

13 Corsi, D. J., & Subramanian, S. V. (2012). Association between socioeconomic status and self-reported diabetes in India: A cross-sectional multilevel analysis. *BMJ Open, 2*(4), e000895. https://doi.org/10.1136/bmjopen-2012-000895

14. Farooq, M., Nawaz, H. H., & Ijaz, A. (2025). Prevalence of gestational diabetes in jobholding and housewives associated with limited awareness of healthcare in Faisalabad. *Journal of Health, Wellness and Community Research*. https://doi.org/10.61919/t0shwj85

15. Lone, A. A. (2019). Agriculture transformation and rural development in Kashmir Valley (with special reference to District Baramulla). *International Journal of Social Science and Economic Research*.

16Feghali, M. N., Abebe, K. Z., Comer, D. M., Caritis, S., Catov, J. M., & Scifres, C. M. (2018). Pregnancy outcomes in women with an early diagnosis of gestational diabetes mellitus. *Diabetes Research and Clinical Practice, 138*, 177–186. https://doi.org/10.1016/j.diabres.2018.02.004

17Feghali, M. N., Abebe, K. Z., Comer, D. M., Caritis, S., Catov, J. M., & Scifres, C. M. (2018). Pregnancy outcomes in women with an early diagnosis of gestational diabetes mellitus. *Diabetes Research and Clinical Practice, 138*, 177–186. https://doi.org/10.1016/j.diabres.2018.02.004

18. Xiang, A. H., Takayanagi, M., Black, M. H., Trigo, E., Lawrence, J. M., Watanabe, R. M., & Buchanan, T. A. (2013). Longitudinal changes in insulin sensitivity and beta cell function between women with and without a history of gestational diabetes mellitus. *Diabetologia, 56*(12), 2753–2760. https://doi.org/10.1007/s00125-013-3048-0

19. Wan, P., Yang, Q., Wang, W., Xie, C., Feng, Q., Wu, L., Liang, Z., Ling, Z., & Liu, F. (2026). Glycated albumin is not applicable to differentiate gestational diabetes mellitus in Chinese pregnant women. *Clinica Chimica Acta, 578*, 120508. https://doi.org/10.1016/j.cca.2025.120508

20. Kampmann, U., Knorr, S., Fuglsang, J., & Ovesen, P. (2019). Determinants of maternal insulin resistance during pregnancy: An updated overview. *Journal of Diabetes Research, 2019*, 5320156. https://doi.org/10.1155/2019/5320156

21Catalano, P. M., & Shankar, K. (2017). Obesity and pregnancy: Mechanisms of short-term and long-term adverse consequences for mother and child. *BMJ, 356*, j1. https://doi.org/10.1136/bmj.j1

22. Chia, C. W., Egan, J. M., & Ferrucci, L. (2018). Age-related changes in glucose metabolism, hyperglycemia, and cardiovascular risk. *Circulation Research, 123*(7), 886–904. https://doi.org/10.1161/CIRCRESAHA.118.312806

23. Li, Y., Ren, X., He, L., Li, J., Zhang, S., & Chen, W. (2020). Maternal age and the risk of gestational diabetes mellitus: A systematic review and meta-analysis of over 120 million participants. *Diabetes Research and Clinical Practice, 162*, 108044. https://doi.org/10.1016/j.diabres.2020.108044

*Association of advancing maternal age with increased severity of gestational diabetes mellitus (gdm) At the time of diagnosis.*

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# PREVALENCE OF METABOLIC DYSFUNCTION–ASSOCIATED STEATOTIC LIVER DISEASE IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AT A TERTIARY CARE HOSPITAL IN ISLAMABAD, PAKISTAN

**Introduction:** Metabolic dysfunction–associated steatotic liver disease (MASLD) is the most common chronic liver disease worldwide and is highly prevalent among individuals with type 2 diabetes mellitus (T2DM). The presence of MASLD in patients with T2DM substantially increases the risk of advanced liver fibrosis, cirrhosis, hepatocellular carcinoma, cardiovascular disease, chronic kidney disease, and all-cause mortality. Despite the growing burden of MASLD in South Asia, local epidemiological data remain limited. This study aimed to determine the prevalence of MASLD and identify its associated cardiometabolic risk factors among patients with T2DM attending a tertiary care hospital in Islamabad, Pakistan.

**Methods:** A hospital-based cross-sectional study was conducted between January and December 2024 involving 450 adult patients with established T2DM. Hepatic steatosis was diagnosed using abdominal ultrasonography. MASLD was defined according to the 2023 international consensus criteria as the presence of hepatic steatosis in individuals with at least one cardiometabolic risk factor. Since all participants had T2DM, they fulfilled the metabolic risk criterion. Demographic, anthropometric, clinical, and biochemical data were collected. Logistic regression analysis was performed to identify independent predictors of MASLD.

**Results:** Among the 450 enrolled patients, 281 were diagnosed with MASLD, yielding a prevalence of 62.4%. Patients with MASLD had significantly higher body mass index, waist circumference, serum triglyceride levels, alanine aminotransferase levels, insulin resistance, and prevalence of hypertension compared with those without MASLD (all $p < 0.001$). Independent predictors of MASLD included body mass index ≥27 kg/m² (OR 2.9; 95% CI 1.9–4.4), triglyceride levels ≥150 mg/dL (OR 1.8; 95% CI 1.2–2.7), and poor glycaemic control (HbA1c ≥7.5%; OR 1.6; 95% CI 1.1–2.4).

**Conclusion:** MASLD is highly prevalent among Pakistani adults with T2DM and is strongly associated with obesity, dyslipidaemia, insulin resistance, and poor glycaemic control. Routine screening for hepatic steatosis and risk stratification for advanced fibrosis should be integrated into diabetes care to facilitate early diagnosis and timely intervention.

**Keywords:** MASLD, Type 2 diabetes mellitus, Hepatic steatosis, Diabetes, Prevalence, Metabolic dysfunction.

## Introduction

Metabolic dysfunction–associated steatotic liver disease (MASLD) has become the most common chronic liver disease globally, affecting approximately 30% of the adult population, with substantially higher prevalence among individuals with obesity and type 2 diabetes mellitus (T2DM). In 2023, an international multi-society Delphi consensus introduced the term MASLD to replace non-alcoholic fatty liver disease (NAFLD), reflecting the central role of metabolic dysfunction in disease pathogenesis and moving away from terminology based primarily on alcohol exclusion. MASLD belongs to the broader spectrum of steatotic liver disease (SLD), while metabolic dysfunction-associated steatohepatitis (MASH) replaces the previous term non-alcoholic steatohepatitis (NASH).

Type 2 diabetes mellitus is one of the strongest risk factors for MASLD. Current evidence indicates that nearly two-thirds of individuals with T2DM have hepatic steatosis, and many are at increased risk of developing advanced fibrosis, cirrhosis, hepatocellular carcinoma, and liver-related mortality. Furthermore, patients with both T2DM and MASLD experience significantly higher rates of cardiovascular disease and chronic kidney disease than individuals with either condition alone. Consequently, major international societies now recommend routine assessment of liver disease risk in patients with T2DM.

The pathogenesis of MASLD is multifactorial and involves insulin resistance, adipose tissue dys-

function, chronic low-grade inflammation, oxidative stress, mitochondrial dysfunction, and genetic susceptibility. Insulin resistance promotes increased hepatic free fatty acid influx and de novo lipogenesis, leading to excessive triglyceride accumulation within hepatocytes. Progressive inflammation and hepatocellular injury may subsequently result in fibrosis, cirrhosis, and hepatocellular carcinoma.

Pakistan is experiencing a rapid increase in the prevalence of T2DM because of urbanization, sedentary lifestyles, dietary changes, and increasing obesity. Although diabetes is highly prevalent, data regarding MASLD among Pakistani patients remain limited, particularly using the updated international nomenclature and diagnostic criteria. Most previous local studies evaluated NAFLD using older definitions, making comparison with contemporary international literature difficult.

Determining the burden of MASLD in Pakistani patients with T2DM is essential for developing appropriate screening strategies and preventive interventions. Early identification of individuals at high risk may facilitate timely lifestyle modification, optimization of metabolic risk factors, and referral for fibrosis assessment before the development of irreversible liver disease.

Therefore, this study aimed to determine the prevalence of MASLD among adults with T2DM attending a tertiary care hospital in Islamabad and to identify the demographic, anthropometric, and metabolic factors independently associated with the presence of MASLD.

## Materials and Methods

### *Study Design and Setting*

This hospital-based cross-sectional study was conducted at the Departments of Endocrinology and Hepatology of a tertiary care teaching hospital in Islamabad, Pakistan, from January 2024 to December 2024. The study was designed to determine the prevalence of metabolic dysfunction–associated steatotic liver disease (MASLD) among adults with type 2 diabetes mellitus (T2DM) and to identify factors associated with its presence.

### *Study Population*

A total of 450 consecutive adult patients with established T2DM attending the outpatient endocrinology clinic during the study period were enrolled using consecutive non-probability sampling.

### *Inclusion Criteria*

Patients fulfilling all of the following criteria were included:

- Age ≥18 years.
- Established diagnosis of T2DM according to the American Diabetes Association (ADA) diagnostic criteria.
- Willingness to participate in the study and provide informed written consent.

### *Exclusion Criteria*

Patients were excluded if they had:

- Significant alcohol consumption (>140 g/week for women or >210 g/week for men).
- Positive hepatitis B surface antigen or hepatitis C virus antibodies.
- Autoimmune liver disease.
- Wilson disease.
- Hemochromatosis.
- Drug-induced liver disease or current use of known steatogenic or hepatotoxic medications.
- Pregnancy.
- Previously diagnosed cirrhosis or hepatocellular carcinoma.
- Any other chronic liver disease that could independently explain hepatic steatosis

### *Data Collection*

After obtaining informed consent, demographic and clinical information was collected using a structured data collection form.

The following variables were recorded:

- Age
- Sex
- Duration of T2DM
- Smoking status
- History of hypertension
- History of dyslipidaemia
- Current antidiabetic medications
- Family history of diabetes
- Presence of cardiovascular disease

Anthropometric Measurements

Anthropometric assessment included:

- Height (cm)
- Weight (kg)
- Body mass index (BMI; kg/m²)
- Waist circumference (cm)

Blood pressure was measured after at least five minutes of rest using a calibrated sphygmomanometer. Two readings were obtained, and the average value was recorded.

### *Laboratory Investigations*

After an overnight fast of at least eight hours, venous blood samples were collected for biochemical analysis.

The following investigations were performed:

- Fasting plasma glucose
- Glycated haemoglobin (HbA1c)

- Serum insulin (where available)
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Total cholesterol
- Triglycerides
- High-density lipoprotein cholesterol (HDL-C)
- Low-density lipoprotein cholesterol (LDL-C)
- Platelet count

Insulin resistance was estimated using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR):

HOMA-IR = [Fasting insulin (μU/mL) × Fasting glucose (mmol/L)] ÷ 22.5

***Diagnosis of MASLD***

Hepatic steatosis was assessed using abdominal ultrasonography performed by experienced consultant radiologists who were blinded to the patients' clinical and laboratory information.

Steatosis was graded as:

- Mild
- Moderate
- Severe

according to standard ultrasonographic criteria based on hepatic echogenicity, visualization of intrahepatic vessels, and posterior beam attenuation.

MASLD was diagnosed according to the 2023 international multi-society consensus definition, which requires:

- Evidence of hepatic steatosis on imaging, and
- At least one cardiometabolic risk factor.

As all enrolled participants had established T2DM, every participant fulfilled the required cardiometabolic criterion. Therefore, patients demonstrating hepatic steatosis on ultrasonography were classified as having MASLD after exclusion of alternative causes of steatotic liver disease.

***Assessment of Liver Fibrosis***

Where complete laboratory data were available, the Fibrosis-4 (FIB-4) index was calculated using age, AST, ALT, and platelet count to estimate the risk of advanced liver fibrosis.

Patients were categorized into low-, intermediate-, or high-risk groups according to currently recommended FIB-4 cut-off values. Patients with intermediate or high FIB-4 scores were considered candidates for further evaluation using transient elastography where clinically indicated.

***Outcome Measures***

The primary outcome was the prevalence of MASLD among patients with T2DM.

Secondary outcomes included identification of demographic, anthropometric, clinical, and biochemical factors independently associated with MASLD.

***Statistical Analysis***

Data were entered and analysed using IBM SPSS Statistics version 26.0.

Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range), depending on data distribution. Categorical variables were expressed as frequencies and percentages.

Comparisons between patients with and without MASLD were performed using:

- Independent Student's t-test or Mann–Whitney U test for continuous variables.
- Chi-square test or Fisher's exact test for categorical variables.

Variables with a p-value <0.10 on univariate analysis, together with clinically relevant covariates, were entered into a multivariable logistic regression model to identify independent predictors of MASLD.

Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. A two-sided p-value <0.05 was considered statistically significant.

***Ethical Considerations***

The study protocol was reviewed and approved by the Institutional Review Board/Ethics Committee of the participating hospital before commencement of the study. Written informed consent was obtained from all participants prior to enrolment. All procedures were conducted in accordance with the ethical principles of the Declaration of Helsinki and applicable institutional guidelines. Participant confidentiality was maintained throughout the study by anonymizing all collected data and restricting access to study records.

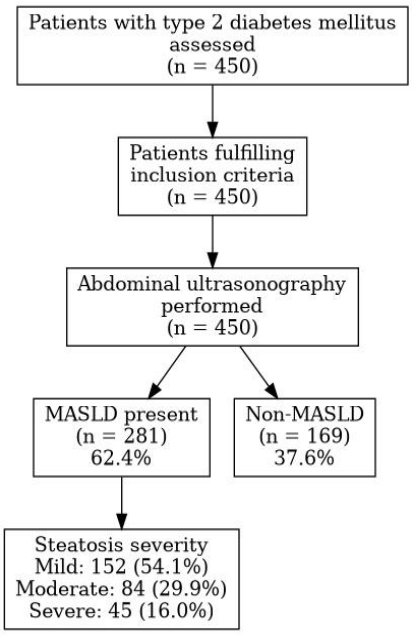
## Results

***Study Population***

A total of 450 adult patients with established type 2 diabetes mellitus (T2DM) were enrolled during the study period. The mean age of the study population was 54.2 ± 10.7 years, and 234 (52.0%) participants were male. The overall mean body mass index (BMI) was 28.1 ± 4.6 kg/m², while the mean duration of diabetes was 8.3 ± 5.1 years.

Ultrasonographic evidence of hepatic steatosis fulfilling the diagnostic criteria for metabolic dysfunction–associated steatotic liver disease (MASLD) was identified in 281 patients, corresponding to an overall prevalence of 62.4%.

**Figure 1**
*Flow diagram of patient recruitment and diagnosis of MASLD among study participants.*




### *Baseline Characteristics*

Patients with MASLD had significantly greater adiposity and a more adverse metabolic profile compared with patients without MASLD. Individuals with MASLD demonstrated significantly higher BMI, waist circumference, serum triglyceride concentrations, alanine aminotransferase (ALT), HbA1c levels, and HOMA-IR values. Hypertension and dyslipidaemia were also significantly more common in the MASLD group.

No statistically significant differences were observed with respect to age or sex distribution between the two groups.

**Table 1**
*Baseline Characteristics of Study Participants*

| Variable | MASLD (n = 281) | Non-MASLD (n = 169) | p-value |
|---|---|---|---|
| Age (years) | 54.8 ± 10.2 | 53.3 ± 11.4 | 0.19 |
| Male sex, n (%) | 150 (53.4) | 84 (49.7) | 0.46 |
| Duration of diabetes (years) | 8.7 ± 5.3 | 7.8 ± 4.8 | 0.08 |
| BMI (kg/m²) | 29.5 ± 4.3 | 25.8 ± 3.7 | <0.001 |
| Waist circumference (cm) | 101.4 ± 9.1 | 92.3 ± 8.4 | <0.001 |
| Hypertension, n (%) | 191 (68.0) | 82 (48.5) | <0.001 |
| Dyslipidaemia, n (%) | 182 (64.8) | 73 (43.2) | <0.001 |
| HbA1c (%) | 8.2 ± 1.4 | 7.5 ± 1.2 | <0.001 |
| ALT (U/L) | 49.2 ± 18.4 | 31.7 ± 12.5 | <0.001 |
| Triglycerides (mg/dL) | 201 ± 68 | 156 ± 52 | <0.001 |
| HOMA-IR | 4.6 ± 1.8 | 2.9 ± 1.2 | <0.001 |

***Prevalence and Severity of MASLD***

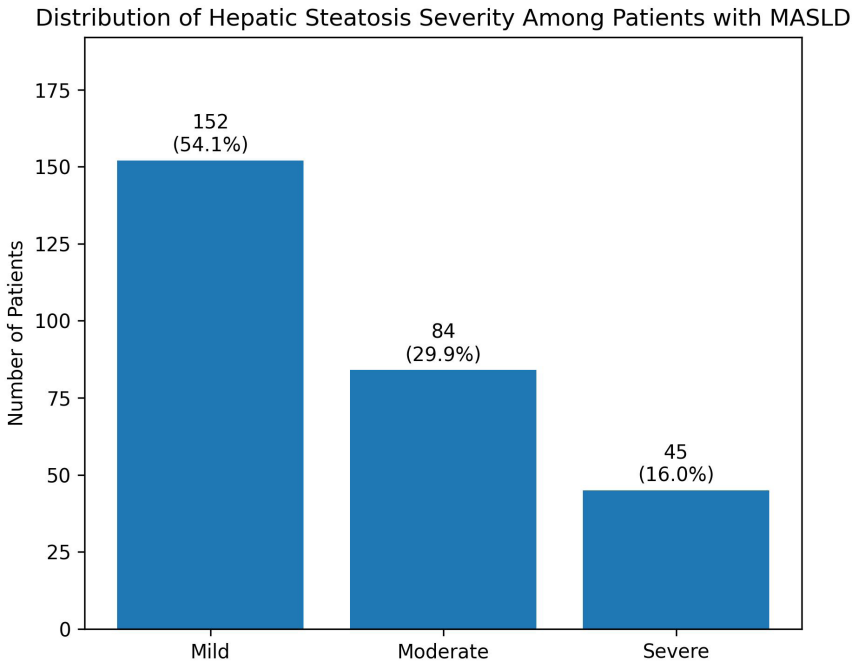
Among the 281 patients diagnosed with MASLD, ultrasonographic grading demonstrated:

- Mild steatosis: 152 patients (54.1%)
- Moderate steatosis: 84 patients (29.9%)
- Severe steatosis: 45 patients (16.0%)

Mild hepatic steatosis represented the most frequently observed grade.

**Figure 2**

*Distribution of hepatic steatosis severity among patients with MASLD*




***Liver Fibrosis Risk Assessment***

FIB-4 scores were calculated for patients with complete laboratory data. Most patients with MASLD were classified as having a low probability of advanced fibrosis. However, a clinically important proportion demonstrated intermediate or high FIB-4 scores, indicating the need for further assessment using transient elastography.

**Table 2**

*Distribution of FIB-4 Risk Categories in Patients with MASLD**

| FIB-4 Category | Number (%) |
|---|---|
| Low risk | 192 (68.3) |
| Intermediate risk | 67 (23.8) |
| High risk | 22 (7.9) |

Calculated for patients with complete laboratory parameters.

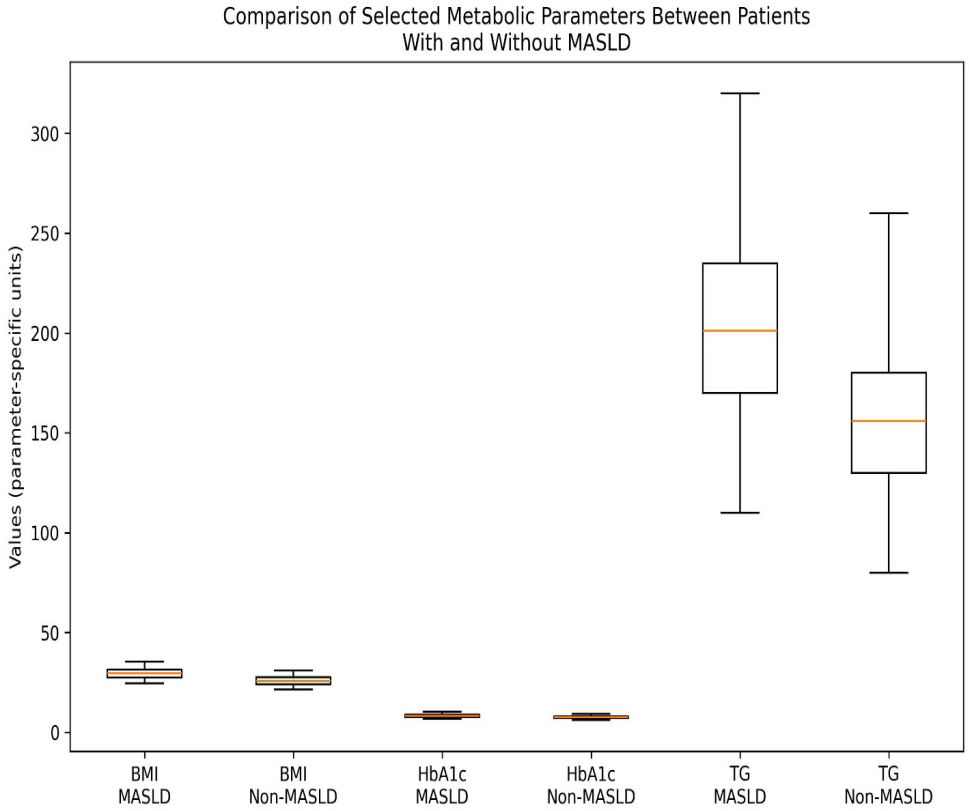
***Factors Associated with MASLD***

On univariate analysis, the presence of MASLD was significantly associated with:

- Higher BMI
- Increased waist circumference
- Elevated serum triglycerides
- Poor glycaemic control (higher HbA1c)
- Elevated ALT
- Increased insulin resistance (HOMA-IR)
- Hypertension
- Dyslipidaemia

No statistically significant association was observed between MASLD and age or sex.

**Figure 3**
*Comparison of selected metabolic parameters between patients with and without MASLD (box plots)*




***Multivariable Logistic Regression Analysis***

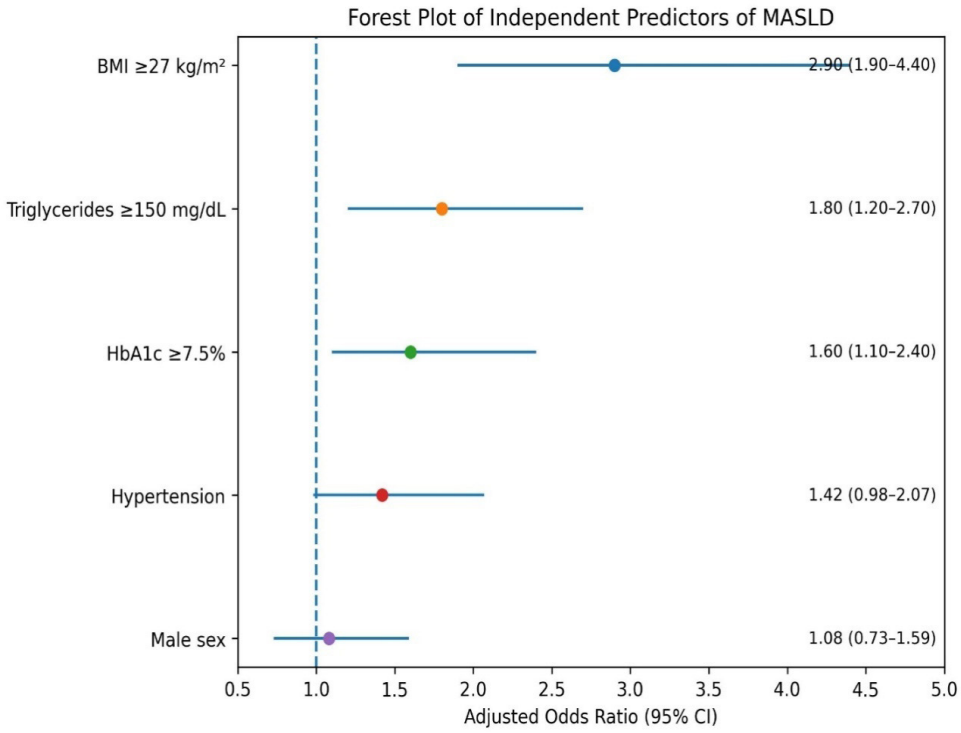
Variables with p <0.10 on univariate analysis were entered into a multivariable logistic regression model.After adjustment for potential confounders, the following variables remained independently associated with MASLD:

Higher BMI was identified as the strongest independent predictor of MASLD in the study population.

**Table 3**
*Independent Predictors of MASLD*

| Variable | Adjusted OR | 95% CI | p-value |
|---|---|---|---|
| BMI ≥27 kg/m² | 2.90 | 1.90–4.40 | <0.001 |
| Triglycerides ≥150 mg/dL | 1.80 | 1.20–2.70 | 0.004 |
| HbA1c ≥7.5% | 1.60 | 1.10–2.40 | 0.019 |
| Hypertension | 1.42 | 0.98–2.07 | 0.063 |
| Male sex | 1.08 | 0.73–1.59 | 0.71 |

**Figure 4**
*Forest plot showing independent predictors of MASLD identified by multivariable logistic regression*




***Summary of Findings***

The present study demonstrated that nearly two-thirds (62.4%) of adults with T2DM had ultrasonographic evidence of MASLD. Patients with MASLD exhibited significantly greater obesity, central adiposity, dyslipidaemia, insulin resistance, and poorer glycaemic control than those without MASLD. Multivariable analysis identified elevated BMI, hypertriglyceridaemia, and poor glycaemic control as independent predictors of MASLD, highlighting the close relationship between metabolic dysfunction and hepatic steatosis in individuals with T2DM.

## Discussion

The present study demonstrated that the prevalence of metabolic dysfunction–associated steatotic liver disease (MASLD) among adults with type 2 diabetes mellitus (T2DM) attending a tertiary care hospital in Islamabad was 62.4%. This finding highlights the substantial burden of hepatic steatosis in Pakistani patients with diabetes and is consistent with contemporary international studies reporting that approximately 60–70% of individuals with T2DM have MASLD.

The recent transition from the term non-alcoholic fatty liver disease (NAFLD) to MASLD represents a significant advancement in the understanding of fatty liver disease. Unlike the previous terminology, MASLD emphasizes the underlying metabolic dysfunction responsible for hepatic steatosis rather than defining the disease by the absence of alcohol consumption. This updated nomenclature more accurately reflects current knowledge regarding disease pathogenesis and improves communication between clinicians, researchers, and patients.

Our observed prevalence is comparable to reports from Europe, North America, and Asia, where MASLD has become increasingly common because of the global epidemics of obesity, insulin resistance, and T2DM. Similar prevalence estimates have also been reported from neighboring South Asian countries, indicating that MASLD has become a major public health concern throughout the region.

A strong association was observed between MASLD and obesity. Patients with MASLD had significantly higher BMI and waist circumference than patients without MASLD, while BMI ≥27 kg/m² emerged as the strongest independent predictor in multivariable analysis. These findings are biological-

ly plausible because excess visceral adiposity contributes to increased free fatty acid flux to the liver, promotes hepatic insulin resistance, and enhances de novo lipogenesis, ultimately leading to triglyceride accumulation within hepatocytes.

Hypertriglyceridaemia was another independent predictor of MASLD in the present study. Elevated circulating triglyceride concentrations reflect the underlying disturbances in lipid metabolism that characterize insulin resistance and metabolic syndrome. Increased hepatic synthesis and impaired clearance of triglyceride-rich lipoproteins further accelerate lipid deposition within the liver. Similar observations have been consistently reported in international cohort studies and systematic reviews.

Poor glycaemic control was also independently associated with MASLD. Patients with HbA1c values ≥7.5% demonstrated a significantly greater likelihood of hepatic steatosis than those with better glycaemic control. Chronic hyperglycaemia promotes oxidative stress, hepatic inflammation, and increased lipogenesis, thereby accelerating progression of steatotic liver disease. Optimizing glycaemic control therefore remains an essential component of MASLD management in patients with T2DM.

Insulin resistance, reflected by significantly higher HOMA-IR values in patients with MASLD, further supports the central role of metabolic dysfunction in disease pathogenesis. Insulin resistance is widely recognized as the principal mechanism linking obesity, T2DM, dyslipidaemia, and hepatic steatosis. Persistent insulin resistance contributes not only to hepatic fat accumulation but also to progressive inflammation, hepatocyte injury, fibrosis, and ultimately cirrhosis.

The higher prevalence of hypertension and dyslipidaemia among patients with MASLD observed in our study further illustrates the close relationship between hepatic steatosis and the broader spectrum of cardiometabolic disease. MASLD is increasingly regarded as a multisystem disorder rather than an isolated liver disease. Individuals with MASLD have an increased risk of cardiovascular disease, chronic kidney disease, heart failure, and overall mortality. In fact, cardiovascular disease remains the leading cause of death in patients with MASLD, emphasizing the importance of comprehensive cardiometabolic risk reduction.

Current international guidelines recommend routine assessment for liver disease in adults with T2DM because diabetes substantially increases the risk of advanced liver fibrosis. Although ultrasonography remains an accessible and practical imaging modality for detecting hepatic steatosis, it cannot reliably determine the degree of fibrosis. Contemporary clinical practice therefore recommends a stepwise approach using simple non-invasive fibrosis scores, such as the Fibrosis-4 (FIB-4) index, followed by transient elastography in patients with intermediate or high fibrosis risk. This strategy enables early identification of individuals who may benefit from specialist hepatology referral while minimizing unnecessary investigations.

The findings of the present study have important clinical implications for Pakistan. Given the increasing prevalence of obesity and T2DM, opportunistic screening for MASLD should be incorporated into routine diabetes care, particularly among individuals with obesity, central adiposity, hypertriglyceridaemia, hypertension, or poor glycaemic control. Early diagnosis provides an opportunity for lifestyle modification, optimization of metabolic risk factors, and timely implementation of pharmacological therapies with demonstrated benefits for both diabetes and liver disease where appropriate.

***Strengths of the Study***

This study is among the first from Pakistan to evaluate hepatic steatosis in patients with T2DM using the updated MASLD nomenclature and contemporary diagnostic framework. The relatively large sample size, standardized ultrasonographic assessment, and comprehensive evaluation of metabolic risk factors enhance the reliability of the findings. Furthermore, the use of multivariable logistic regression enabled identification of independent predictors while adjusting for potential confounding variables.

***Limitations***

Several limitations should be acknowledged. First, the cross-sectional design precludes determination of causal relationships between metabolic risk factors and MASLD. Second, hepatic steatosis was diagnosed using ultrasonography rather than magnetic resonance imaging or liver biopsy, although ultrasonography remains an accepted first-line diagnostic modality in routine clinical practice. Third, the study was conducted at a single tertiary care centre, which may limit the generalizability of the findings to the broader Pakistani population. Finally, advanced fibrosis was not confirmed using transient elastography or histopathological examination, and longitudinal follow-up was not available to evaluate disease progression.

Future multicentre prospective studies incorporating non-invasive fibrosis assessment, transient elastography, and long-term clinical outcomes are warranted to better characterize the natural histo-

ry of MASLD among Pakistani individuals with T2DM.

Overall, the present study demonstrates that MASLD represents a major metabolic comorbidity among patients with T2DM in Pakistan. The close association between MASLD and obesity, insulin resistance, hypertriglyceridaemia, and poor glycaemic control reinforces the importance of integrated multidisciplinary management. Early detection and comprehensive metabolic risk reduction may help prevent progression to advanced liver fibrosis while simultaneously reducing cardiovascular morbidity and mortality.

## Gratitude / conflict of interest

Statement on the Use of Generative AI and AI-Powered Technologies in the Writing Process. Authors declared that GenAi did not used in writing process.

**Refrences**

1. Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, et al. A multi-society Delphi consensus statement on new fatty liver disease nomenclature. Hepatology. 2023;78(6):1966–1986.
2. Eslam M, Sanyal AJ, George J, et al. MAFLD: A consensus-driven proposed nomenclature for metabolic associated fatty liver disease. Gastroenterology. 2020;158(7):1999–2014.e1.
3. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, et al. AASLD Practice Guidance on the clinical assessment and management of metabolic dysfunction-associated steatotic liver disease. Hepatology. 2024.
4. European Association for the Study of the Liver (EASL). EASL Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). J Hepatol. 2024.
5. American Diabetes Association Professional Practice Committee. Standards of Care in Diabetes—2025. Diabetes Care. 2025;48(Suppl 1).
6. Younossi ZM, Golabi P, Paik JM, et al. Global epidemiology of metabolic dysfunction-associated steatotic liver disease. Nat Rev Gastroenterol Hepatol. 2024.
7. Targher G, Byrne CD, Tilg H. MASLD and type 2 diabetes: Pathophysiological links and clinical implications. Lancet Diabetes Endocrinol. 2024.
8. Powell EE, Wong VW, Rinella M. Non-invasive assessment of liver fibrosis in MASLD. J Hepatol. 2024.
9. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of NAFLD—Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64(1):73–84.
10. Targher G, Byrne CD. Clinical review: Non-alcoholic fatty liver disease and type 2 diabetes mellitus. Lancet Diabetes Endocrinol. 2018;6(5):389–398.
11. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: Practice guidance. Hepatology. 2018;67(1):328–357.
12. Marchesini G, Bugianesi E, Forlani G, et al. Non-alcoholic fatty liver disease, steatohepatitis and the metabolic syndrome. Hepatology. 2003;37(4):917–923.
13. Yki-Järvinen H. Non-alcoholic fatty liver disease as a cause and consequence of metabolic syndrome. Lancet Diabetes Endocrinol. 2014;2(11):901–910.
14. Loomba R, Sanyal AJ. The global burden of fatty liver disease. Nat Rev Gastroenterol Hepatol. 2013;10(11):686–690.
15. Das K, Das K, Mukherjee PS, et al. Non-alcoholic fatty liver disease in South Asia: An increasing public health problem. J Clin Exp Hepatol. 2015;5(1):40–51.
16. Raza SA, et al. Ultrasonographic detection of fatty liver disease among patients with type 2 diabetes mellitus in Pakistan. Pak J Med Sci. 2021;37(3):790–795.
17. Ahmed MH, Abu EO, Byrne CD. Non-alcoholic fatty liver disease in the Middle East and South Asia: Epidemiology and clinical implications. World J Hepatol. 2015;7(10):1129–1135.
18. Basit A, Fawwad A, Qureshi H, Shera AS. Prevalence of diabetes, pre-diabetes and associated risk factors in Pakistan. Diabetes Res Clin Pract. 2018;137:230–238.
19. Kim D, Adejumo AC, Yoo ER, et al. Trends in mortality among patients with fatty liver disease and diabetes. Gastroenterology. 2019;156(2):461–472.
20. Lonardo A, Nascimbeni F, Ballestri S, et al. Cardiovascular disease and metabolic dysfunction-associated fatty liver disease: An updated review. Metabolism. 2022;126:154925.

*Prevalence of metabolic dysfunction–associated steatotic liver disease in patients with type 2 diabetes mellitus at a tertiary care hospital in islamabad, pakistan.*

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# WHAT IS THE MOLECULAR BASIS OF GLIOMA? INSIGHTS INTO BIOMARKERS, METABOLIC REPROGRAMMING, AND EMERGING TREATMENT STRATEGIES

**Relevance:** The new classification of central nervous system (CNS) tumors by the World Health Organization (WHO) based on the histological and molecular features allowed a new area for research. Molecular classification of brain cancer is based on the isocitrate dehydrogenase (IDH) enzyme, which is crucial in converting isocitrate into alpha-ketoglutarate during the citric acid cycle.

**The study aimed to** provide an overview of the classification of CNS by WHO and diagnostic methods of brain tumors.

**Results:** The article describes brain tumor diagnostic methods, including tissue biopsy, magnetic resonance imaging (MRI), and liquid biopsy, and reviews molecular biomarkers comprising alterations of genes associated with gliomas and epigenetic changes that reduce the expression of particular genes. The authors consider how these findings can be used in treatment.

**Conclusion:** Molecular reprogramming in cells with mutated IDH causes neomorphic mutations, which leads to changes abundance of alpha-ketoglutarate (αKG) and D-2-hydroxyglutarate (D-2-HG), an increase which stimulates the formation of tumors. Targeted therapies can reduce the concentration of this oncometabolite in cells.

**Keywords:** glioma, glioblastoma, isocitrate dehydrogenase (IDH), D-2-hydroxyglutarate (D-2-HG).

## Introduction

Glioma is a type of brain cancer that arises from the glial cells that support the neurons in the brain. It is a devastating disease that is difficult to treat, and the prognosis for patients with glioma is often poor. They are the most common primary brain tumors, accounting for approximately 80% of all malignant brain tumors [1]. Until 2016 subtypes of glial cells, in which neoplasms grow, classified gliomas into astrocytoma, glioblastoma, oligodendroglioma, and ependymoma. There are four grades of glioma and glioblastoma (GBM) is an IV-class glioma with the lowest survival rate of 5% after 5 years after diagnosis [2].

**Aim:** In the following review, we aimed to provide an overview of molecular classification of brain tumors and propose treatment strategies depending on the mutation type.

Materials and methods: A comprehensive literature search was performed to identify relevant articles on the classification of CNS tumors, biomarkers, changes in metabolic pathways, and possible treatment strategies. The search was carried out in various electronic databases, including PubMed, Scopus and Web of Science. The search was limited to articles published between 2007 and 2023 to ensure that the most recent and relevant research in this area is included. The initial search yielded a total of 75 articles. The received papers were checked based on their titles and abstracts to assess their relevance to the topic of interest. As a result, research papers focusing on the molecular aspects of glioma, biomarkers, metabolic reprogramming, and potential treatment strategies were included. Articles were excluded, if they were not in English, or were not directly related to the specific objectives of this review article. After review, 37 articles were selected, con-

taining various study designs, including in vitro and in vivo experiments, and clinical studies.

**Results and discussion:**

*CNS tumor classification.*

CNS tumor classification suggested by WHO in 2007 was based on histological features of tumour cells[3] Rapidly developing molecular techniques demanded new classification, and as a result in 2016, when along with histogenesis, molecular features were taken into account by WHO. For example, while in 2007 classification of diffuse gliomas placed astrocytoma, oligodendroglioma, and oligoastrocytoma into separate groups based on their histology, in 2016 astrocytoma, oligodendroglioma, and oligoastrocytoma with mutant and wild-type IDH gene, p/19q codeletion and not otherwise specified designation (not enough molecular data) was in the same group [3].

In 2021 [4] classification added even more details on its molecular aspects, including changes in DNA sequences like IDH1 and IDH2, TP53 and H3 histone mutations, TERT promotor mutation [5], and EGFR gene amplification. Also, the importance of distinguishing adult and children gliomas led to the formation of the following groups in the last classification: 1) adult-type diffuse gliomas, 2) pediatric-type diffuse low-grade gliomas, 3) pediatric-type diffuse high-grade gliomas, and 4) circumscribed astrocytic gliomas. Apart from changes in the sequence of DNA, epigenetic changes also were taken into account, and methylation tests are suggested to be utilised as a part of a diagnostics procedure along with sequencing, FISH, and assays to assess molecular changes [5].

Appropriate classification and observation of clinical characteristics are required to study any pattern and suggest treatment strategies depending on the brain tumor type. Changes in classification of CNS tumour show that genetic mutations in tumors are becoming key factors in diagnosis, prognosis, and treatment planning.

*Diagnostics.*

Advances in genetic testing have led to the identification of specific DNA mutations that are associated with glioma, and these mutations can be used for personalized treatments.

Traditionally, the detection of glioma mutations has been based on tissue biopsy samples to observe its histology and DNA mutations. However, it is known as an invasive and sometimes impossible method due to the difficulty to access of deeper layers of the brain. Moreover, repeated biopsies are required to make a reliable diagnosis, and suggest treatment strategies.

As an alternative less invasive strategy imaging techniques such as MRI can be used. Imaging can be used to track responses to therapies reflecting the changes in size [6]. However, it is not specific and can be used only as part of diagnostics to provide information about the presence, size, and histological type of brain tumor [7], for further identification of nature and improved diagnosis, molecular analysis is necessary [8]

*Molecular diagnostics*.

Liquid biopsies, which involve analyzing DNA in bodily fluids, are emerging as a promising tool for diagnosing and monitoring glioma. Some studies compared strategies of identification mutations in DNA and confirmed a high concordance of results between DNA isolation from circulating tumour DNA in body fluids and standard tissue biopsies [9]. *They could accurately detect glioma-specific mutations* in blood plasma [10], serum [11], cerebrospinal fluid [12–22], and saliva [23] to identify mutations in a patient's DNA at earlier stages than some imaging techniques [24]. Body fluids are directly exposed to tumor tissue in the brain and contain DNA fragments that are shed from the tumor cells in the brain. Extracellular DNA may appear in body liquids as a result of direct splitting off from tumour cells, phagocytic activity, necrosis, and apoptosis. As tumour cells are not stable, they release more circulating DNA compared to healthy patients, which can be a primary indicator of tumour. [25] Sources of nucleic acid in body liquids are cell-free DNA, cell-free RNA, and circulating tumor cell DNA [24], the length of which is shorter than the genome and usually varies between 140 [23] and 21000 base pairs [25]. As the aforementioned diagnostic method, liquid biopsies also have a number of limitations as low concentration of circulating tumour DNA and this method is applicable only for specific types of tumour depending on their location and properties of affected tissues [23].

Identifying biomarkers that can predict the prognosis of patients with glioma is an important area of research. Gene malfunction can be caused by either mutation or gene expression alterations. All grade III and grade IV tumours are treated by surgery and the following chemotherapy, mostly alkylating chemotherapy, which prevents protein synthesis and cell division [26]. Depending on the mutated gene, the response to chemotherapy may vary, this led to molecular classification of tumours. However, it is

important to keep in mind that multiple biomarkers should be used for better management.

*Gene alterations*

Based on the major genetic alterations including IDH mutation and 1p/19q co-deletion, gliomas can be classified into three subtypes [27]: IDH mutation; mutant IDH, and 1p/19q codeletion; wild-type IDH. IDH gene is important in diagnostics and management strategies because according to WHO IDH is mutated in >80% of clinical cases with grade IV secondary glioblastomas and <10% of primary glioblastomas [28]. Also, mutations in many other genes, associated with gliomas, correlate with IDH mutation. Thus, mutations in ATRX, TP53 gene, and 1p/19q co-deletion are rare in wild-type IDH [27], while mutations in TERT promoter, EGFR, and H3-3A gene are more common in wild-type IDH [2]. However, TERT and EGFR mutations cannot be a biomarker for glioma [29]. Moreover, patients with mutated IDH have less severe symptoms, a better prognosis than wild-type, and a better response to temozolomide. Thus, the overall survival period of glioblastoma patients with IDH1 mutations with a median survival of 3.8 years compared to 1.1 years of patients with wild-type IDH1 [30]. However, these patients often struggle with epilepsy [31]. Patients with both IDH mutation and 1p/19q co-deletion have the best prognosis. 1p/19q co-deletion is rarely found with wild-type IDH and is crucial in the diagnosis of oligodendroglioma [27]. So, this classification helps to predict survival and propose treatment strategies.

The function of telomerase reverse transcriptase (TERT) is telomere lengthening. Normally, telomeres shorten after each DNA replication causing cellular aging. However, mutations in codons C228T and C250T enhance the expression of transcription factors by creating a novel binding site for transcriptional enhancers, causing the length of telomeres to increase and making the cell immortal, which is considered a hallmark of oncogenesis. There is no observed association between TERT promoter mutations and other mutations such as IDH and TP53 [32].

The epidermal growth factor receptor (EGFR) was amplified or mutated in up to 60% of cases in glioblastoma patients. EGFR interacts with transcription factors causing a cascade of reactions that promotes growth [33].

*Epigenetics*

MGMT (enzyme O6-methylguanine-DNA methyltransferase) promoter methylation is also common in glioblastoma patients and has a low survival rate [2]. The methylation status of the MGMT promoter has gained significant importance as a key factor in determining prognosis and predicting the response to Temozolomide (TMZ). TMZ is an alkylating agent that induces DNA damage by introducing methyl groups to specific positions on guanine and adenine. Individuals with MGMT expression resulting from an unmethylated promoter or other mechanisms are likely to exhibit a limited response to conventional alkylating therapy. [27,34]

Overexpression of another gene, which is called SOX (sex-determining part of Y chromosome) could be used as a biomarker to identify GBM. Additionally, SOX2 may enhance the ability of glioma cells to migrate and invade surrounding tissues. Consequently, SOX2 shows promise as a potential target for therapeutic interventions in GBM patients, but further experiments are required to clearly understand the specific mechanism by which SOX contributes to the development of GBM [35]

*Metabolic reprogramming.*

Metabolic reprogramming of cells is the main characteristic of tumour. There are three IDH isoforms: IDH1, IDH2, and IDH3 with the same functions. The former is in a cellular cytoplasm while, the two others are inside mitochondria, where the Citric acid cycle takes place. Wild-type isocitrate dehydrogenase 1 is an enzyme that catalyzes the reaction of decarboxylation of isocitrate forming alpha-ketoglutarate (αKG) in the Citric acid cycle during cellular respiration.

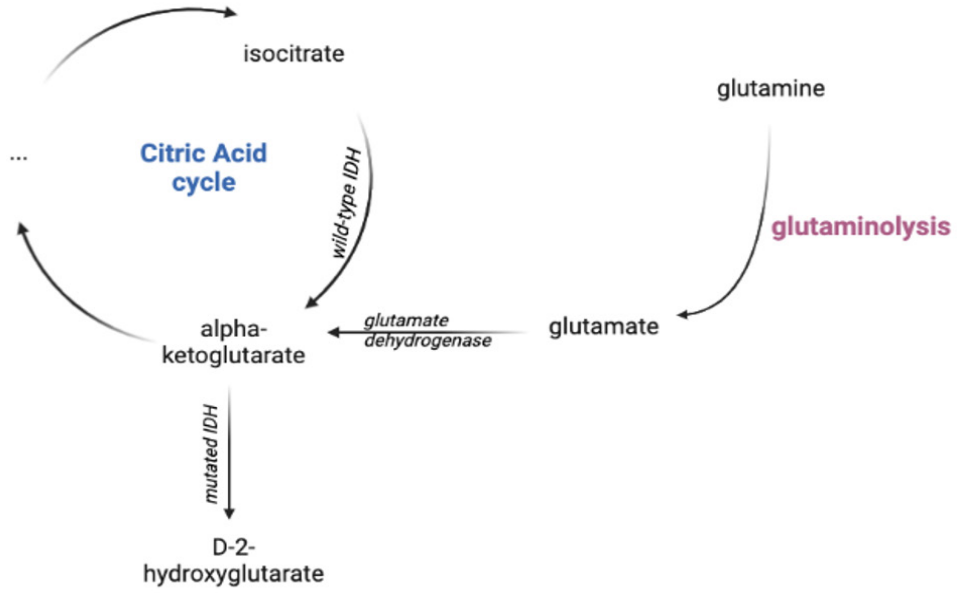
In most glioma cases because of point mutation arginine is substituted with other amino acids, which leads to the decreased affinity of IDH to isocitrate as a result of conformational changes in a structure of a protein. Instead, in individuals with both mutated alleles, the enzyme is inactive. The function of heterozygotes alters, and IDH with one mutated allele converts αKG to D-2-hydroxyglutarate (D-2-HG) using reduced nicotinamide adenine dinucleotide phosphate (NADPH) as a co-factor. It leads to the lack of the αKG and the accumulation of D-2-HG oncometabolite. Accumulation of 2-HG disrupts cellular processes, contributes to DNA hypermethylation, and promotes tumorigenesis. Interestingly, D-2-HG has no known function in mammals during homeostasis, and its concentration normally is low <300 μM, and produced as a result of mistakes in metabolism, hence can be used as a pharmacodynamic marker [28].

These changes cause metabolic reprogramming and alter the source of αKG to the glutamine pathway by glutamate dehydrogenase [36]. That is the reason why mutated IDH has a better response to the inhibition of the glutaminolysis pathway, as a

result inhibiting the conversion of glutamine to glutamate and hence, glutamate into αKG [37] (figure 1). Another reason for slow-growing IDH mutant glioma is an accumulation of D-2-HG that causes hypermethylation of genes that regulate enzymes that participate in glycolysis, the first step of cellular respiration [36].

Thus, as the Citric acid cycle is altered, and glutaminolysis and glycolysis pathways are inhibited, lower energy is produced for cellular functions such as cell division and growth, which is unfavorable for the spread of tumour cells. Understanding the biochemical changes happening in mutated cells helps to implement targeted therapies for tumor treatment.

**Figure 1**
*Simplified reprogrammed pathway with mutated IDH allele (created with Biorender, an online tool for biological figures by authors)*




The current treatment options for brain cancers, regardless of their molecular characteristics, remain limited. The standard approach involves surgical removal, when feasible, followed by postoperative radiation and chemotherapy with adjuvant temozolomide. Despite advances in understanding the genetics of brain cancer, still, the median survival of patients with glioblastoma is still low. That is why an appropriate and efficient treatment strategy should be found.

*Targeted Therapies*

Targeted therapies, which are drugs that specifically target certain molecules or genetic mutations in cancer cells, are also being studied for the treatment of glioma. As IDH mutations cause the accumulation of D-2-HG, therapeutic strategies are targeted to reduce the amount of oncometabolite. IDH inhibitors have emerged as a promising therapeutic approach in the treatment of glioblastoma (GBM). These small molecule inhibitors specifically target the abnormal activity of mutant IDH enzymes, aiming to restore their normal function and reduce the levels of 2-hydroxyglutarate (2-HG). By doing so, they aim to inhibit aberrant cell growth and induce cellular differentiation in GBM cells harboring IDH mutations. Clinical trials investigating IDH inhibitors, including ivosidenib and vorasidenib, have shown encouraging outcomes, including improved overall survival and manageable side effects. Combination Therapies: IDH inhibitors can also be combined with other treatment modalities to enhance their efficacy. Preclinical studies have shown that combining IDH inhibitors with radiation therapy or chemotherapy agents, such as temozolomide, can produce synergistic effects. These combination approaches target multiple pathways simultaneously, potentially overcoming

resistance mechanisms and improving treatment outcomes. [36].

*Challenges and Future Directions.*

While IDH-targeted therapies hold great promise, several challenges need to be addressed for their successful implementation in GBM treatment:

- Patient Selection: Proper patient selection is crucial, as IDH mutations are not present in all GBM cases. Accurate identification of IDH-mutant GBM through molecular profiling is essential to ensure that patients who can benefit from IDH-targeted therapies receive appropriate treatment.

- Resistance Mechanisms: Resistance to IDH inhibitors can develop over time, limiting their long-term effectiveness. Further research is needed to elucidate the underlying resistance mechanisms and develop strategies to overcome or prevent resistance.

- Combination Strategies: Identifying the optimal combination partners for IDH inhibitors and determining the most effective treatment regimens require extensive preclinical and clinical investigation.

## Conclusion

In conclusion, the new classification of CNS tumors based on histological and molecular features has provided a valuable framework for research in the field. The molecular classification, particularly involving the IDH enzyme, has emerged as a crucial factor in understanding brain cancer. Notably, the neomorphic mutations occurring in cells with mutated IDH have been identified as key contributors to tumor formation, leading to alterations in the abundance of alpha-ketoglutarate and D-2-HG. Elevated levels of D-2-HG have been implicated in promoting tumorigenesis. Thus, targeted therapies aimed at reducing the concentration of this oncometabolite in cells hold promise as a potential treatment approach. The integration of molecular insights into the classification and management of CNS tumors has opened up new possibilities for personalized and targeted therapies. Further research and clinical studies are warranted to explore the full potential of these targeted treatments and to develop effective strategies for reducing the impact of IDH mutations in brain cancer patients.

**References**

1. Ostrom, Q. T., Cioffi, G., Waite, K., Kruchko, C., & Barnholtz-Sloan, J. S. (2021). *CBTRUS statistical report: Primary brain and other central nervous system tumors diagnosed in the United States in 2014–2018*. *Neuro-Oncology, 23*(12 Suppl. 2), iii1–iii105. https://doi.org/10.1093/neuonc/noab200

2. Zhang, P., Xia, Q., Liu, L., Li, S., & Dong, L. (2020). *Current opinion on molecular characterization for GBM classification in guiding clinical diagnosis, prognosis, and therapy*. *Frontiers in Molecular Biosciences, 7*, 562798. https://doi.org/10.3389/fmolb.2020.562798

3. Louis, D. N., Perry, A., Reifenberger, G., von Deimling, A., Figarella-Branger, D., Cavenee, W. K., Ohgaki, H., Wiestler, O. D., Kleihues, P., & Ellison, D. W. (2016). The 2016 World Health Organization Classification of Tumors of the Central Nervous System: A summary. Acta Neuropathologica, 131(6), 803–820. https://doi.org/10.1007/s00401-016-1545-1

4. Osborn, A. G., Louis, D. N., Poussaint, T. Y., Linscott, L. L., & Salzman, K. L. (2022). The 2021 World Health Organization Classification of Tumors of the Central Nervous System: What neuroradiologists need to know. American Journal of Neuroradiology, 43(7), 928–937. https://doi.org/10.3174/AJNR.A7462

5. uratli, T. A., Stasik, S., Zolal, A., Schuster, C., Richter, S., Daubner, D., Shankar, G. M., Williams, G. H., Jones, P. S., Moulin, T. C., & Weller, M. (2018). TERT promoter mutation detection in cell-free tumor-derived DNA in patients with IDH wild-type glioblastomas: A pilot prospective study. Clinical Cancer Research, 24(21), 5282–5291. https://doi.org/10.1158/1078-0432.CCR-18-0601

6Bouzón, A., Acea, B., Soler, R., Iglesias, Á., Santiago, P., Mosquera, J., Varela, J. R., & Calvo, L. (2016). Diagnostic accuracy of MRI to evaluate tumour response and residual tumour size after neoadjuvant chemotherapy in breast cancer patients. Radiology and Oncology, 50(1), 73–79. https://doi.org/10.1515/raon-2016-0006

7. Abd-Ellah, M. K., Awad, A. I., Khalaf, A. A. M., & Hamed, H. F. A. (2019). A review on brain tumor diagnosis from MRI images: Practical implications, key achievements, and lessons learned. Magnetic Resonance Imaging, 61, 300–318. https://doi.org/10.1016/j.mri.2019.05.028.

8Li, Y., Sui, Y., Chi, M., Zhang, J., & Guo, L. (2021). Study on the effect of MRI in the diagnosis of benign and malignant thoracic tumors. Disease Markers, 2021, Article 5569270. https://doi.org/10.1155/2021/5569270

9. Wyatt, A. W., Annala, M., Aggarwal, R., Beja, K., Feng, F. Y., Youngren, J., Foye, A., Lloyd, P., Nykter, M., Beer, T. M., Alumkal, J. J., & Chi, K. N. (2017). Concordance of circulating tumor DNA and matched metastatic tissue biopsy in prostate cancer. Journal of the National Cancer Institute, 109(12), djx118. https://doi.org/10.1093/jnci/djx118

10. Bettegowda, C., Sausen, M., Leary, R. J., Kinde, I., Wang, Y., Agrawal, N., Bartlett, B. R., Wang, H., Luber, B., Alani, R. M., Antonarakis, E. S., Azad, N. S., Bardelli, A., Brem, H., Cameron, J. L., Lee, C. C., Fecher, L. A., Gallia, G. L., Gibbs, P., … Diaz,

L. A., Jr. (2014). Detection of circulating tumor DNA in early- and late-stage human malignancies. Science Translational Medicine, 6(224), 224ra24. https://doi.org/10.1126/scitranslmed.3007094

11. Sabedot, T. S., Malta, T. M., Snyder, J., Nelson, K., Wells, M., deCarvalho, A. C., Mukherjee, A., Chitale, D., Mosella, M. S., Sokolov, A., Del Maestro, R. F., Colman, H., Sulman, E. P., Verhaak, R. G. W., Noushmehr, H., & Network of Investigators. (2021). A serum-based DNA methylation assay provides accurate detection of glioma. Neuro-Oncology, 23(9), 1494–1508. https://doi.org/10.1093/neuonc/noab040

12. Weston, C. L., Glantz, M. J., & Connor, J. R. (2011). Detection of cancer cells in the cerebrospinal fluid: Current methods and future directions. Fluids and Barriers of the CNS, 8(1), 14. https://doi.org/10.1186/2045-8118-8-14

13. Mouliere, F., Mair, R., Chandrananda, D., Marass, F., Smith, C. G., Su, J., Morris, J., Watts, C., Brindle, K. M., Rosenfeld, N., & Mair, K. (2018). Detection of cell-free DNA fragmentation and copy number alterations in cerebrospinal fluid from glioma patients. EMBO Molecular Medicine, 10(12), e9323. https://doi.org/10.15252/emmm.201809323

14. Ma, C., Yang, X., Xing, W., Yu, H., Si, T., & Guo, Z. (2020). Detection of circulating tumor DNA from non-small cell lung cancer brain metastasis in cerebrospinal fluid samples. Thoracic Cancer, 11(3), 588–593. https://doi.org/10.1111/1759-7714.13300

15. Escudero, L., Martínez-Ricarte, F., & Seoane, J. (2021). ctDNA-based liquid biopsy of cerebrospinal fluid in brain cancer. Cancers, 13(9), 1989. https://doi.org/10.3390/cancers13091989

16. Zhao, Z., Zhang, C., Li, M., Shen, Y., Feng, S., & Liu, J. (2020). Applications of cerebrospinal fluid circulating tumor DNA in the diagnosis of gliomas. Japanese Journal of Clinical Oncology, 50(3), 325–332. https://doi.org/10.1093/jjco/hyz183

17 Sun, Y., Li, M., Ren, S., Liu, Y., Zhang, J., Li, S., Wang, X., Zhang, H., Wang, J., & Wang, Y. (2021). Exploring genetic alterations in circulating tumor DNA from cerebrospinal fluid of pediatric medulloblastoma. Scientific Reports, 11(1), 5638. https://doi.org/10.1038/s41598-021-85075-0

18. Escudero, L., Llort, A., Arias, A., Díaz-Navarro, A., Martínez-Ricarte, F., Rubio-Pérez, C., Hernández-Tejero, M., Fuster-García, E., Cordero, E., Vidal, A., & Seoane, J. (2020). Circulating tumour DNA from the cerebrospinal fluid allows the characterisation and monitoring of medulloblastoma. Nature Communications, 11(1), 5376. https://doi.org/10.1038/s41467-020-19175-0

19. Fontanilles, M., Deniel, A., Marguet, F., Beaussire, L., Magne, N., Derrey, S., Di Fiore, F., Laquerrière, A., Freger, P., Dubessy, A.-L., & Sabourin, J.-C. (2022). Usefulness of circulating tumor DNA from cerebrospinal fluid in recurrent high-grade glioma. Revue Neurologique, 178(9), 975–980. https://doi.org/10.1016/j.neurol.2022.02.008

20. Simonelli, M., Dipasquale, A., Orzan, F., Lorenzi, E., Persico, P., Navarria, P., Pessina, F., Bello, L., DiMeco, F., Santoro, A., & Miozzo, M. (2020). Cerebrospinal fluid tumor DNA for liquid biopsy in glioma patients' management: Close to the clinic? Critical Reviews in Oncology/Hematology, 146, 102879. https://doi.org/10.1016/j.critrevonc.2019.102879

21. Ballester, L. Y., Glitza Oliva, I. C., Douse, D. Y., Chen, M. M., Lan, C., Haydu, L. E., Lazar, A. J., Torres-Cabala, C. A., Bassett, R. L., Royal, R. E., Hwu, W.-J., Davies, M. A., Patel, S. P., Hwu, P., Wargo, J. A., Tetzlaff, M. T., & Curry, J. L. (2018). Evaluating circulating tumor DNA from the cerebrospinal fluid of patients with melanoma and leptomeningeal disease. Journal of Neuropathology & Experimental Neurology, 77(7), 628–635. https://doi.org/10.1093/jnen/nly033

22. Orzan, F., de Bacco, F., Lazzarini, E., Crisafulli, G., Gasparini, A., Dipasquale, A., Simonelli, M., Persico, P., Pessina, F., Bello, L., DiMeco, F., Santoro, A., Bardelli, A., & Miozzo, M. (2023). Liquid biopsy of cerebrospinal fluid enables selective profiling of glioma molecular subtypes at first clinical presentation. Clinical Cancer Research, 29(8), 1577–1589. https://doi.org/10.1158/1078-0432.CCR-22-2860

23 Tivey, A., Church, M., Rothwell, D., Dive, C., & Cook, N. (2022). Circulating tumour DNA—Looking beyond the blood. Nature Reviews Clinical Oncology, 19(9), 600–612. https://doi.org/10.1038/s41571-022-00636-9

24. Ilié, M., & Hofman, P. (2016). Pros: Can tissue biopsy be replaced by liquid biopsy? Translational Lung Cancer Research, 5(4), 420–423. https://doi.org/10.21037/tlcr.2016.07.13

25. Quraish, R., Hirahata, T., Quraish, A., & Quraish, S. (2023). An overview: Genetic tumor markers for early detection and current gene therapy strategies. Cancer Informatics, 22, 11769351231171047. https://doi.org/10.1177/11769351231171047

26 Ralhan, R., & Kaur, J. (2007). *Alkylating agents and cancer therapy*. *Expert Opinion on Therapeutic Patents, 17*(9), 1061–1075. https://doi.org/10.1517/13543776.17.9.1061

27. Horbinski, C., Nabors, L. B., Portnow, J., Baehring, J., Bhatia, A., Bloch, O., Butowski, N., Chiocca, E. A., Chu, R., Fabiano, A. J., Fink, K., Hattangadi-Gluth, J., Holdhoff, M., Kaley, T., Kumthekar, P., Lo, S. S., Mrugala, M. M., Olar, A., Puduvalli, V. K., … Wen, P. Y. (2023). NCCN Guidelines® Insights: Central nervous system cancers, Version 2.2022. Journal of the National Comprehensive Cancer Network, 21(1), 12–20. https://doi.org/10.6004/jnccn.2023.0002

28. Dang, L., Yen, K., & Attar, E. C. (2016). IDH mutations in cancer and progress toward development of targeted therapeutics. Annals of Oncology, 27(4), 599–608. https://doi.org/10.1093/annonc/mdw013

29. Ma, S., Rudra, S., Campian, J. L., Dahiya, S., Dunn, G. P., Johanns, T. M., Ansstas, G., Kim, A. H., Huang, J., Perry, A., & Khasraw, M. (2020). Prognostic impact of CDKN2A/B deletion, TERT mutation, and EGFR amplification on histological and molecular IDH-wildtype glioblastoma. Neuro-Oncology Advances, 2(1), vdaa126. https://doi.org/10.1093/noajnl/vdaa126

30. Parsons, D. W., Jones, S., Zhang, X., Lin, J. C. H., Leary, R. J., Angenendt, P., Mankoo, P., Carter, H., Siu, I.-M., Gallia, G. L., Olivi, A., McLendon, R., Rasheed, B. A., Keir, S., Nikolskaya, T., Nikolsky, Y., Busam, D. A., Tekleab, H., Diaz, L. A., Jr., … Velculescu, V. E. (2008). An integrated genomic analysis of human glioblastoma multiforme. Science, 321(5897), 1807–1812. https://doi.org/10.1126/science.1164382

31. Derks, J., Kulik, S., Wesseling, P., Numan, T., Hillebrand, A., van Dellen, E., Klein, M., Reijneveld, J. C., Stam, C. J., & Douw, L. (2019). Understanding cognitive functioning in glioma patients: The relevance of IDH-mutation status and functional connectivity. Brain and Behavior, 9(4), e01204. https://doi.org/10.1002/brb3.1204

32. Powter, B., Jeffreys, S. A., Sareen, H., Cooper, A., Brungs, D., Po, J., Roberts, T. L., Koh, E. S., Scott, K. F., Wheeler, H. R., Simes, J., Lee, C. K., & Brown, M. P. (2021). Human TERT promoter mutations as a prognostic biomarker in glioma. Journal of Cancer Research and Clinical Oncology, 147(4), 1007–1017. https://doi.org/10.1007/s00432-020-03425-4

33. Liu, F., Hon, G. C., Villa, G. R., Turner, K. M., Ikegami, S., Yang, H., Ye, Z., Li, B., Kuan, S., Lee, A. Y., Zanca, C., Wei, B., Lucey, G., Shieh, A. W., Kwok, R., Huse, J. T., Cooper, L. A. D., Sulman, E. P., Bettegowda, C., … Mischel, P. S. (2015). EGFR mutation promotes glioblastoma through epigenome and transcription factor network remodeling. Molecular Cell, 60(2), 307–318. https://doi.org/10.1016/j.molcel.2015.09.002

34. Butler, M., Pongor, L., Su, Y. T., Xi, L., Raffeld, M., Quezado, M., Trepel, J. B., Aldape, K., Pommier, Y., Wu, J., & Ji, J. (2020). MGMT status as a clinical biomarker in glioblastoma. Trends in Cancer, 6(5), 380–391. https://doi.org/10.1016/j.trecan.2020.02.010

35. Pan, C., Liang, L., Wang, Z., Zhang, B., Li, Q., Tian, Y., Zhang, Y., Wang, J., Zhao, Y., & Jin, Y. (2022). Expression and significance of SOX B1 genes in glioblastoma multiforme patients. Journal of Cellular and Molecular Medicine, 26(3), 789–799. https://doi.org/10.1111/jcmm.17135

36. Han, S., Liu, Y., Cai, S. J., Qian, M., Ding, J., Larion, M., Gilbert, M. R., & Yang, C. (2020). IDH mutation in glioma: Molecular mechanisms and potential therapeutic targets. British Journal of Cancer, 122(11), 1580–1589. https://doi.org/10.1038/s41416-020-0814-x

37 Choi, Y. K., & Park, K. G. (2018). Targeting glutamine metabolism for cancer treatment. Biomolecules & Therapeutics, 26(1), 19–28. https://doi.org/10.4062/biomolther.2017.178

*What is the molecular basis of glioma? Insights into biomarkers, metabolic reprogramming, and emerging treatment strategies*

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# KNOWLEDGE, ATTITUDES AND BEHAVIOR OF STUDENTS IN RELATION OF MENTAL HEALTH: A CROSS-SECTIONAL STUDY IN KAZAKHSTAN

**Introduction:** Attitudes of students to mental health issues is a neglected area in Kazakhstan due to high level of stigmatization, cultural traditions and lay beliefs as in some other countries. We did an attempt to recognize issues related to knowledge, attitude and behavior of students of first year (17-19 years old) regarding mental health issues on the base of self-administered questionnaire across the country.
**Methods:** A self-administered questionnaire was the main tool for data collection. The whole questionnaire consists of three main parts: 1) healthy life style; 2) harmful habits (smoking, alcohol and drug use); 3) mental health. Total sample size was 5,000 students from five regions of the country.
**Results**: One of the main results of this study was relatively high percentage of 17-19 years old students who understand importance of healthy lifestyle and reported about their readiness to follow it. Only a few proportion of students consider "good" mental health as a part of healthy lifestyle. Young people mostly think that physical activity and refusal of bad harmful habits (smoking, alcohol and drug use) are main components of healthy lifestyle.
**Conclusion:** The majority of students tend to improve their health. Students reported about their confidence in governmental clinics, specialists and desire to obtain information about health during trainings, competitions and festivals at university settings.
**Keywords:** students, students' mental health, stigmatization, attitudes and behavior.

## Introduction

Youth health is one of the important directions of public health due to many reasons, including high psychological and intellectual load connected with significant social, economic and physical changes in life, lack of emotional stability and hormonal maturity (1, 2). In addition, this period of life for many young people is characterized by intensive study at university or college, an active search for a model of behavior and lifestyle, which is often accompanied by acquisition of such bad habits as the use of tobacco, alcohol, drugs and other forms of risky behavior, including suicidal (3, 4).Despite on positive role of higher education for career and personal growth, the educational process itself is a serious factor affecting the lifestyle and health of young people (4,5). Also, in Kazakhstan, as in many countries of the world, the bachelor / mastereducational system introduced at universities also increased psychological burden on students (6, 7, 8,9).

A number of studies from around the world demonstrated that studying at universities can cause stress, leading to a deterioration in both physical and mental health (4, 6, 9). Traditionally, the studentship isconsidered as a short transitional period in people's lives. Analysis of publications onstudents' health and wealth revealed deterioration of health during study (5, 6). According to the data health of students is declining from first to final year of study. The deterioration of students' health occurs due to above mentioned reasons, as well as due to the complex impact of unfavorable learning factors, characterized by intensification of mental activity, increased educational load, shortage of self-study time in the learning process.

The UNICEF's study conducted in Kazakhstan identified high risks to the mental health of young people, including depression and suicidal behavior (10).

Research studies on students' mental health in Kazakhstan and in other countries of former Sovi-

et Union are rare and usually are conducted within a single university (8, 10). Attitudes of students to mental health issues is a neglected area in Kazakhstan due to high level of stigmatization, cultural traditions and lay beliefs as in some other countries (10, 11, 12, 13). We did an attempt to recognize issues related to knowledge and attitude of studentsof first year (17-19 years old) regarding mental health issues on the base of self-administered questionnaire across the country.

## Methods and materials

A self-administered questionnaire was the main tool for data collection. The whole questionnaire consists of three main parts: 1) healthy life style; 2) harmful habits (smoking, alcohol and drug use); 3) mental health.

Questionnaires were constructed to measure parameters related to three components: cognitive (knowledge and awareness); emotional (attitude); behavioral (action). Before data collection there was a focus group discussion to assess clarity and quality of translation (between Kazakh and Russian languages) among bilingual students (two groups with 12 students in each).

The total sample size was 5000 students from five regions of the country. We choose them according to geographical position (central part, south, west, north and east), cultural features, and high density of student population (colleges and universities). It was a cross-sectional descriptive study.

Informed consents were provided by students and their parents (for students who were younger than 18). Students were required to complete self-administered questionnaires offline and online within 30-40 minutes.

## Results

The study involved5,000 respondents from five regions of Kazakhstan aged 17-19 years ( 60% were females and 40% were males), and covered Kazakh and Russian speaking students. The majority of students (56%) were from urban settings, 27% – from rural area and 17% – from urban-type settlements (UGT) or sub-urban area. Most of the respondents (53.5%)live in dormitories, 27.4 % – with their parents, 12.2% with relatives and 6.9% in rental housing. All personal data were provided by students' offices of the universities.

***Healthy life style***

Approximately one third of the respondents think that healthy lifestyle is related to physical activity and refusal of harmful habits such as smoking, alcohol and drugs(Table 1). Only 6% of the interviewed students classifiedability to manage emotions and being in harmony with themselves as a healthy lifestyle skill.Very low percentage of respondents (5%)think that good quality sleep is important to stay healthy. Majority of students indicated they consider adherence to principles of healthy lifestyle as important part of the lives (Table 1).

According to derived data students obtain information about healthy lifestyle from their parents (29%), from Internet sources (23%), from university staff (22%) and from the mass-media (20%) (Table 1).

**Table 1**
*Answers of students about healthy lifestyle (N= 5,000; p< 0.05)*

| | % | SE |
|---|---|---|
| What is healthy lifestyle? | | |
| Refusal of bad habits | 30.0 | 0.6 |
| Healthy Food | 18.0 | 0.5 |
| Compliance with daily regimen | 13.0 | 0.5 |
| Compliance with hygiene | 16.0 | 0.5 |
| Good quality sleep | 5.0 | 0.3 |
| Physical activity and sport | 31.0 | 0.7 |
| Stress management and coping skills | 6.0 | 0.3 |
| Do you consider it necessary to adhere to the principles of healthy lifestyle? | | |
| Yes, of course | 61.0 | 0.7 |
| May be | 34.0 | 0.7 |

*Continuation of the table*

| | % | SE |
|---|---|---|
| I don't think so | 5.0 | 0.3 |
| What are yourinformation sources about healthy lifestyle? | | |
| From teachers and administration of university | 22.0 | 0.6 |
| Mass-media | 20.0 | 0.6 |
| Internet resources | 23.0 | 0.6 |
| Peers | 8.0 | 0.4 |
| Medical workers | 11.0 | 0.4 |
| Parents | 29.0 | 0.6 |

***Harmful habits (smoking, alcohol and drug use)***

Table 2 demonstrates results regarding alcohol consumption, smoking and drug use among students of 1-st year. Respondents also provided their ideas about why young people start to smoke, drink alcohol and use drugs: "self-affirmation, desire to be "cool", "influence of bad company, coercion", "curiosity and new sensations".

If students have problems with smoking, alcohol or drug use, then more than half of the respondents will visit specialists of governmental clinics. None of the responding adolescents chose the option that they would "turn to their parents". In addition, students provided short narratives for this question. They were: "this will not happen to me", "there is no need", "there will be no such need", "there are no problems, and there will not be".

Respondents also provided answers about measures can be used to protect young people from tobacco smoking, alcoholism, drug use (Table 2). The majority of participants prefer trainings at university settings. With regard to other types of measures the answers were almost evenly distributed (Table 2).

**Table 2**

*Answers of students about alcohol, tobacco and drugs consumption (N=5,000; p< 0.05)*

| | % | SE |
|---|---|---|
| Do you consume alcohol? | | |
| Never | 88,0 | 0.5 |
| Sometimes | 9,0 | 0.4 |
| Regularly | 3,0 | 0.2 |
| Do you smoke? | | |
| Never | 85,0 | 0.5 |
| Used to smoke but now quit | 6,0 | 0.3 |
| Sometimes | 6,0 | 0.3 |
| Regularly | 3,0 | 0.2 |
| Do you use drugs? | | |
| Never | 100,0 | - |
| Used to consume but not now | - | - |
| Sometimes | - | - |
| Regularly | - | - |
| What are the reasons why young people start consume alcohol, smoke and use drugs? | | |
| Conflicts with parents | 22,0 | 0.5 |
| Curiosity and new sensations | 20,0 | 0.7 |

*Continuation of the table*

| | % | SE |
|---|---|---|
| Influence of bad company, coercion | 23,0 | 0.6 |
| Problems with peers | 8,0 | 0.4 |
| Despair, psychological stress, loneliness | 11,0 | 0.5 |
| Self-affirmation, desire to be “cool” | 29,0 | 0.5 |
| Where do you go in case of problems with alcohol, tobacco and drug use? | | |
| To specialists of governmental clinics | 53,0 | 0.7 |
| To specialists of private clinics and NGOs | 11,0 | 0.4 |
| Rehabilitation centers | 14,0 | 0.5 |
| Parents | - | - |
| University staff | 6,0 | 0.3 |
| Religious representatives | 4,0 | 0.3 |
| Nowhere, to no one | 12,0 | 0.5 |
| What actions can protect young people from problems with alcohol, tobacco and drug use? | | |
| Trainings on prevention at university settings | 26,0 | 0.6 |
| Demonstration of videos, photo, posters in public places | 16,0 | 0.5 |
| Counselling of psychologist | 13,0 | 0.5 |
| Group meetings with specialists | 16,0 | 0.5 |
| Campaigns, performances | 12,0 | 0.5 |
| Mass-media, movies, talk-shows | 16,0 | 0.5 |

***Mental health***

Table 3 demonstrates answers of respondents to questions related to mental health issues. More than 60% of students have positive feelings about beauty, harmony and life. The majority of students(76%) are satisfied with their relations with their parents and only one percent of respondents do not feel comfortably in their relationships with their parents (Table 3). The main reasons for conflicts in the family, according to students are misunderstanding (46%), rudeness (18%), refusal to participate in family affairs (14%), alcohol consumption (10%).

**Table 3**

*Answers of students about mental health (N=5,000; p< 0.05)*

| | % | SE |
|---|---|---|
| How often do you experience a sense of harmony, a sense of beauty, a feeling that life, nature or something else is beautiful? | | |
| Very often | 17,0 | 0.7 |
| Often | 45,0 | 0.5 |
| Rarely | 26,0 | 0.6 |
| Very rarely | 9,0 | 0.4 |
| Never | 3,0 | 0.2 |
| Are you comfortable with your relationship with your parents? | | |
| Yes | 76,0 | 0.6 |
| Mainly, yes | 12,0 | 0.5 |
| In some ways yes, in others not | 9,0 | 0.4 |
| Mostly no | 3,0 | 0.2 |

*Continuation of the table*

| | | |
|---|---|---|
| No | 1,0 | 0.1 |
| Are you comfortable with your relationship with your peers? | | |
| Yes | 62,0 | 0.7 |
| Mainly, yes | 18,0 | 0.5 |
| In some ways yes, in others not | 15,0 | 0.5 |
| Mostly no | 4,0 | 0.3 |
| No | 1,0 | 0.1 |
| Are you comfortable with your relationship with university staff ? | | |
| Yes | 44,0 | 0.7 |
| Mainly, yes | 16,0 | 0.5 |
| In some ways yes, in others not | 29,0 | 0.6 |
| Mostly no | 9,0 | 0.4 |
| No | 2,0 | 0.2 |
| In the event of a conflict or some unpleasant situation, are you able to take a pull on yourself and calm down ? | | |
| Yes | 55,0 | 0.7 |
| Sometimes not | 23,0 | 0.6 |
| Mostly no | 7,0 | 0.4 |
| No | 2,0 | 0.2 |
| If at university (or other place) you find yourself involved in a conflict situation, how do you try to resolve it? | | |
| Long discussions in which you stubbornly defend your position | 31,0 | 0.7 |
| Indifferentremovalfromdisputes | 29,0 | 0.7 |
| A clear statement of their position and refusal to further disputes | 37,0 | 0.7 |
| I don't know | 3,0 | 0.1 |
| Do you get the feeling that nobody needs you? | | |
| Yes | 12,0 | 0.7 |
| Rather yes than no | 19,0 | 0.6 |
| More likely no than yes | 22,0 | 0.6 |
| No | 47,0 | 0.5 |
| Do problems that arise often seem insoluble to you? | | |
| Yes | 12,0 | 0.5 |
| Rather yes than no | 10,0 | 0.4 |
| More likely no than yes | 26,0 | 0.6 |
| No | 52,0 | 0.7 |

Mainly, students have good relationships with peers, e.g. 62% are completely satisfied with their communication with peers (Table 3). The majority of the respondents (62%) answered that they are satisfied with the relationship with their peers. To the question «In the event of a conflict or some unpleasant situation, are you able to take a pull on yourself and calm down ?» more than half of the interviewed students answered in the affirmative way, 32% of the respondents answered that they could not pull themselves together and calm down on their own. According to the derived data, young people usually try to solve a conflict through long discussions (31%) or a through clear statement of their position (37%).

Comfort in relationships with academic staff of universities varies from "yes" to "no": from 44% to 2%.

Almost half of respondents (46%) did not get feelings "that nobody needs you?». But one third of students experienced such kind of feelings (Table 3).

Half of the respondents categorically denied the existence of insoluble problems in their lives. Other part of students noted the presence of insoluble problems to varying degrees in different periods of their lives.

## Discussion

One of the main results of this study was relatively high percentage of 17-19 years old students who understand importance of healthy lifestyle and reported about their readiness to follow it. Furthermore, students understand harm of smoking, alcohol and drugs and have a desire to be treated in case of addictions. Simultaneously, merely a few proportion of students consider "good" mental health as a part of healthy lifestyle. Young people mostly think that only physical activity and refusal of bad harmful habits (smoking, alcohol and drug use) are main components of healthy lifestyle. Mental health and appropriate skills mainly is not subject for broad discussion and is not related to healthy lifestyle. It can be explained by stigmatization of mental health issues and heritage of Soviet period (8, 9). Mental health issues are associated with psychiatric diagnoses related to "madness" (8, 11)). For that reason in our questionnaire we avoided such words as "mental health", "psychological issues", "depression". The majority of respondents informed about their ability to cope with serious situations, to stay calm, to find constructive decisions in conflictsand other similar situations.However, there were answers demonstrated existence of students with undeveloped skills to cope with severe situations and mental issues. That was an important information regarding necessity of psychological support for students. Some authors support an idea to provide psychological aid and services within university settings (2, 14). Many programs on mental health promotion were developed by universities in different countries (14, 15, 16). Promising project "Mentally Health Universities" was introduced in the British universities in 2019. The evaluation demonstrated a positive experience of the Mentally Healthy Universities program among staff and students of pilot universities (16, 17).

Thus, programs on mental health promotion in university settings demonstrated positive impact not only on students but also on staff. The main issue for Kazakhstan universities is overcoming stigma about mental health issues among administration of universities and Ministry of Education and Science. As an alternative we can recommend introduction of one of existing programs on mental health promotion, and after adaptation to introduce in a pilot university in Kazakhstan. In addition, services on mental health promotion should be available also to foreign students (18, 19, 20).

### Limitations

All data on gender, age, living places of students were provided by students' offices, therefore we were not able to conduct more profound analysis of database due to isolated personal data of students. Also we did not include questions on risks of suicidal behavior due to stigmatization of mental health issues and suicides.

## Conclusion

In general, Kazakhstan students have a positive attitude about healthy life style and ready to follow it. At the same time they do not consider mental health promotion as a part of healthy life style. In addition, students are aware about harm of smoking, alcohol and drug use. They have an intension to improve their health. Students reported about their confidence in governmental clinics, specialists and desire to obtain information about health during trainings, competitions and festivals at university settings.

### Ethical considerations

Ethical issues (including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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### Conflicts of Interest

The authors declare that there is no conflict of interest.

**Refrences**

1. World Health Organization Regional Office for Europe. (2007). *Principles for the protection of persons with mental illness and the improvement of mental health care*. https://www.euro.who.int/mentalhealth/declarations/20061204_

2. Lange, M., Löwe, A., Stassen, G., et al. (2021). Health literacy, health status and health behaviors of German students: Study protocol for the "Healthy Habits" cohort study. *BMC Public Health, 21*, 152. https://doi.org/10.1186/s12889-021-11542-w

3. Lange, M., Löwe, A., Stassen, G., et al. (2021). Health literacy, health status and health behaviors of German students: Study protocol for the "Healthy Habits" cohort study. *BMC Public Health, 21*, 152. https://doi.org/10.1186/s12889-021-11542-w

4. Widyasari, D., & Turnip, S. (2019). Does healthy lifestyle contribute to physical and mental health among university students? *Makara Journal of Health Research, 23*(3), 150–156.

5. Liu, Y., Li, B., Hao, F., et al. (2021). Associations between borderline personality disorder features and the risk of first onset major depressive disorder: Findings from a 2-year longitudinal study in a sample of first-year university students in China. *Journal of Affective Disorders, 295*, 5–10.

6. Zakharova, R., Timofeyeva, A., Mikhaiylova, A., & Timofeyev, L. (2014). The evaluation of health condition of first year students. *Problemy Sotsialnoi Gigieny, Zdravookhraneniia i Istorii Meditsiny, 4*, 6–8.

7. Ermakova, N., Melnichenko, P., Prokhorov, N., Timoshenko, K., Matveev, A., Kostina, E., & Minnibaev, T. (2016). Lifestyle and health of students. *Gigiena i Sanitaria, 95*(6), 558–563.

8. Saifullina, N. (2015). Educational process and health of students. *Meditsina i Ekologiia, 4*, 95–98.

9. Ludwig, A., Burton, W., Weingarten, J., Milan, F., Myers, D., & Kliger, B. (2015). Depression and stress amongst undergraduate medical students. *BMC Medical Education, 15*, 141. https://doi.org/10.1186/s12909-015-0425-z

10. United Nations Children's Fund (UNICEF). (2014). *UNICEF study on prevalence, underlying causes, risk and protective factors in respect to suicides and attempted suicides in Kazakhstan*.

11. Corrigan, P., & Watson, A. (2002). Understanding the impact of stigma on people with mental illness. *World Psychiatry, 1*(1), 16–20.

12. Masedo, A., Grandón, P., Saldivia, S., et al. (2021). A multicentric study on stigma towards people with mental illness in health sciences students. *BMC Medical Education, 21*, 324. https://doi.org/10.1186/s12909-021-02695-8

13. Yamaguchi, S., Mino, Y., & Uddin, S. (2011). Strategies and future attempts to reduce stigmatization and increase awareness of mental health problems among young people: A narrative review of educational interventions. *Psychiatry and Clinical Neurosciences, 65*, 405–415.

14. Ahorsu, D., Sánchez Vidaña, D., Lipardo, D., et al. (2021). Effect of a peer-led intervention combining mental health promotion with coping-strategy-based workshops on mental health awareness, help-seeking behavior, and wellbeing among university students in Hong Kong. *International Journal of Mental Health Systems, 15*, 6. https://doi.org/10.1186/s13033-020-00432-0

15Byrne, R., & Morrison, A. (2010). Young people at risk of psychosis: A user-led exploration of interpersonal relationships and communication of psychological difficulties. *Early Intervention in Psychiatry, 4*, 162–168.

Mind. (2020). *Mentally healthy universities: Year one. Interim evaluation report*.

17. Ibrayeva, Z., Aldyngurov, D., Myssayev, A., & Kassym, L. (2017). The influence of cultural stress on the health status of foreign students: Literature review. *Medical Journal of Western Kazakhstan, 56*(4), 21–26.

18. Zubair, M. D., Tukinova, A., & Mussabekova, Z. (2026). A study of medical students' perceptions and knowledge of climate change and its impact on health. *International Journal of Adolescent Medicine and Health, 38*(1), 61–71. https://doi.org/10.1515/ijamh-2025-0069

19. Sleiay, M., Othman, A. A., Sleiay, B., et al. (2026). Sleep quality, mental health, lifestyle factors, and academic performance among medical students in three Syrian universities: A cross-sectional study. *Discover Mental Health, 6*, 29. https://doi.org/10.1007/s44192-026-00377-9

20. Yazhini, K., Kapoor, P., Minhas, D., Kundu, M., Gongadi, H., & Prusty, R. (2025). Investigation on integrating fundamental activities and interventions for students' mental and psychosocial welfare in education. *Multidisciplinary Reviews, 8*, 2025ss0425. https://doi.org/10.31893/multirev.2025ss0425

*Knowledge, attitudes and behavior of students in relation of mental health: a cross-sectional study in Kazakhstan*

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- Keywords / phrases – number of words 3-7.

**Next page (new):**

**The name of all sections is shown in bold lowercase letters on the left. Original articles.**

- **Introduction** consists of the following main elements:

▪ Justification of the choice of topic; relevance of the topic or problem. In substantiating the choice of a topic based on a description of the predecessors experience, a problematic situation is reported (the absence of any research, the appearance of a new object, etc.). The relevance of the topic is determined by the general interest in the knowledge of this object, but the lack of comprehensive answers to existing questions, it is proved by the theoretical or practical significance of the topic.

▪ Definition of the object, subject, goals, objectives, methods, approaches, hypotheses and the significance of your work. The purpose of the study is related to the proof of the thesis, that is, the presentation of the subject of research in the aspect chosen by the author.

- **Material and Methods** – should consist of a description of the materials and the progress of work, as well as a full description of the methods used.

▪ Characterization or description of the research material includes its presentation in qualitative and quantitative terms. The characteristic of the material is one of the factors determining the reliability of conclusions and research methods.

▪ This section describes how the problem was studied: detailed information without repeating previously published established procedures; identification of equipment (software) and a description of materials are used, with the obligatory introduction of novelty when using materials and methods.

The scientific methodology should include:

- research question (s);
- put forward hypothesis (thesis);
- stages of the study;
- research methods;
- research results.

- The **Results and Discussion** section provides an analysis and discussion of the research results you received. A conclusion is drawn on the results obtained during the study, the main essence is revealed. And this is one of the most important sections of the article. It is necessary to analyze the results of its work and discuss the relevant results in comparison with previous works, analyzes and conclusions.
- **Conclusions, findings** – summarizing and integrating the work at this stage; confirmation of the truth of the statement made by the author, and the author's conclusion on the change in scientific knowledge, taking into account the results. The conclusions should not be abstract, they should be used to summarize the results of the study in a particular scientific field, with a description of the proposals or possibilities for further work.

- The structure of the conclusion should contain the following questions: What are the goals and methods of the study? What are the results? What are the findings? What are the prospects and opportunities for implementation, application development?

- In the literature review section, fundamental and new works on the studied topics of foreign authors in English should be covered (at least 15 works), an analysis of these works in terms of their scientific contribution, as well as research gaps that you supplement in your article.

▪ IT IS UNACCEPTABLE to have many links that are not related to work, or inappropriate judgments about your own achievements, links to your previous works.

The list of used literature, or the Bibliographic list consists of at least 5 titles of literature for a clinical case 15 titles for other options for articles, and of the total number of foreign authors should be at least 50%. If there are works presented in the Cyrillic alphabet in the list of literature, it is necessary to present the list of literature in two versions: the first in the original, the second in the Romanized alphabet (transliteration).

▪ **The romanized list of literature** should look like this: author (s) (transliteration – translit.ru) → (year in parentheses) → title of the article in transliterated version [translation of the title of the article in English in square brackets], name of the Russian-language source (transliteration, or English name – if any), output with designations in English.

**For example:** Gokhberg L., Kuznetsova T. (2011) Strategiya-2020: novye kontury rossiiskoi innovatsionnoi politiki [Strategy 2020: New Outlines of Innovation Policy]. Foresight-Russia, vol. 5, no 4, pp. 8-30. The list of references is presented in alphabetical order, and ONLY those works that are cited in the text.

▪ The design style of the Romanized list of literature, as well as sources in English (another foreign) language for socio-humanitarian areas – the American Psychological Association (http://www.apastyle.org/), for science and technology – Chicago Style (www.chicagomanualofstyle. org).

▪ In the bibliographic list

▪ References to cited works in the text of the socio-humanitarian direction are given in brackets, indicating the first author of the work, year of publication: page number (s). For example, (Zalessky 1991: 25). If there are several works of the same author in the list of literature published in one year, then in addition to the year of publication, the letter “a”, “b”, etc. For example, (Saduova, 2001a: 15), (Saduova, 2001b, 22). For natural science articles, links are made out in square brackets with numbering as the cited works appear in the text.

- **All abbreviations and acronyms** must be deciphered at first use in the text, with the exception of well-known abbreviations and acronyms.

**For bibliographic references, you can also use the Mendeley Reference Manager.**

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