BMC Pharmacology and Toxicology

RESEARCH

Open Access

Past use of metformin is associated with increased risk of myelodysplastic syndrome development in diabetes mellitus patients: a cross-sectional study of 54,869 patients

Tamer Hellou[1,2†], Guy Dumanis[3†], Shir Portugez[4], Aviv Philip Goncharov[5], Eden Trodler[5], Asaf Stern[5], Imanuel Carlebach[5], Omer Kahlon[5], Maysan Abu Jwella[5], Ekram Nimer[6], Ahlam Athamna[7], Aya Berman[8], Gad Segal[2,9*] and Reut Kassif Lerner[2,10]

Abstract

Background Myelodysplastic Syndrome (MDS) is a devastating hematologic malignancy associated with advanced age. Diabetes Mellitus (DM) is one of the most common morbidities worldwide, with metformin serving as the first line therapy for several decades. However, the potential association between previous metformin use and the risk of developing MDS remains uncertain.

Methods This cross-sectional study addressed the possible association between prior metformin use in DM patients and the subsequent development of MDS.

Results Data from 54,869 DM patients was retrieved from their medical records from a tertiary medical center. Of these, 20,318 patients had been exposed at some point in time to metformin, with 133 (0.7%) subsequently developing MDS. In contrast, among 34,551 DM patients with no prior exposure to metformin, only 154 (0.4%) developed MDS later in life. The Odds Ratio (OR) for MDS development amongst metformin users compared to the entire study population was 1.48 (95% CI 1.17–1.86; $p=0.001$). A multivariate analysis adjusting for gender, age, congestive heart failure and chronic kidney disease, past exposure to metformin remained an independent risk factor for MDS development (OR = 1.6, 95% CI 1.26–2.03; $p<0.001$).

Conclusion Previous exposure to metformin amongst DM patients is associated with an increased risk for MDS development later in life. This is a preliminary, cross-sectional study that show that larger studies in variable MDS patient populations are warranted.

†Tamer Hellou and Guy Dumanis equal contribution.

*Correspondence:
Gad Segal
gad.segal@sheba.health.gov.il

Full list of author information is available at the end of the article

Keywords Biguanides, Myelodysplastic syndrome, MDS, Metformin, Odds ratio, Cross sectional study

Introduction

Myelodysplastic syndrome, a disease with significant clinical impact and financial burden

Myelodysplastic syndrome (MDS) refers to a group of fatal hematologic conditions characterized by various chromosomal anomalies and point mutations. It affects the elderly and is rare under the age of 70 years [1–3]. The syndrome is marked by inefficient hematopoiesis, various degrees of cytopenia, and dysplasia of one or more cellular lineages [4]. The exact causes and underlying pathophysiological mechanisms remain poorly understood. In contrast to acute leukemia, MDS is clinically defined by a lower percentage of blasts in peripheral blood smears, though there is a persistent risk of progression to frank leukemia. In clinical practice, two types of classifications are used to describe MDS: the World Health Organization (WHO) classification and the International Consensus Classification (ICC) [5]. Both classifications are based on genetic anomalies within the nucleus and morphological anomalies in affected cells. Another important staging system is the Revised International Prognostic Scoring System (IPSS-R) which stratify patients according to their risk of disease progression into low- and high-risk categories [6]. While MDS may affect multiple cell lines, the red cell linage is the most commonly affected, with 80–85% of MDS patients presenting with anemia [7]. Other clinical manifestations are dependent on other defects in cellular lineages, including high susceptibility to infections in cases of neutropenia and mucosal or petechial bleeding in patients with thrombocytopenia [8].

In addition to laboratory findings, MDS is associated with significant clinical and financial burdens. a decline in quality of life has been described by several studies, including that by Oliva et al. that evaluated the quality of life in both low-risk and high-risk MDS patients. They found that most patients in both groups reported fatigue, nausea, vomiting, emotional stress, depression, and sleep disturbances [5]. In a separate study by Kota et al., 26.9% of high-risk MDS patients treated with first-line therapies, such as Azacitidine and Decitabine, developed acute myeloid leukemia (AML) within the first year of treatment. The mean overall survival (OS) was 14.9 months in these 861 high-risk MDS patients. Intriguingly, high-risk patients developed AML more rapidly in the years following initiation of first-line treatment [9].

MDS patients also experience a considerably greater financial burden than those without cancer. Shafrin et al. (2019) reported monthly expenses for MDS patients that are 3 times higher compared to cancer-free controls. The increased costs are mainly due to higher hospitalization rates and pharmaceutical expenses associated with MDS treatment [10].

Risk factors for MDS development

Although most MDS cases are classified as idiopathic, previous studies have established associations between various harmful factors and increased risk of MDS. These factors include treatments such as alkylating agents, topoisomerase II inhibitors and azathioprine, as well as chemicals like benzene, radiotherapy, and/or chemotherapy, with increased risk for hematologic malignancies in general and MDS development in particular [11–16]. Recent studies have also linked tobacco consumption, various autoimmune disorders, and antituberculosis drugs to a higher risk of developing MDS [17]. Additionally, some occupational exposures could also be associated with MDS, notably agricultural workers, textile operators, healthcare professionals, and machine operators [18].

Metformin—history and mechanisms of action

Metformin, a dimethyl biguanide, is a key oral medication for lowering blood glucose levels in type 2 diabetes. Its history goes back to *Galega officinalis*, a traditional European herb rich in guanidine, known to lower blood sugar since 1918. Guanidine derivatives, composed of biguanides, were synthesized, and used to treat diabetes in the 1920s and 1930s, but their use was stopped due to severe toxicity and the emergence of insulin in the late 1970s [19, 20].

The long-term cardiovascular benefits of metformin were demonstrated in the 1998 UK Prospective Diabetes Study (UKPDS), establishing it as first-line treatment for diabetes. Until recently, metformin was the most commonly prescribed drug world for lowering blood glucose levels and still holds potential for additional therapeutic applications [19, 20].

The American Diabetes Association (ADA), a key authority in diabetes management, provides recommendations for pharmacologic therapy in adults with type 2 diabetes. It emphasizes the importance of healthy lifestyle behaviors and considers comorbidities and treatment goals when selecting medications. The ADA suggests using agents that reduce cardiorenal risk for patients with atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease. According to updated ADA guidelines, early combination therapy of metformin in conjunction with insulin may help delay treatment failure [21].

Metformin's main site of action is the liver, influencing major pathways of hepatic gluconeogenesis and

glycogenolysis, ultimately reducing glucose levels in the blood. Metformin, presumably, alters gluconeogenesis and fatty acid synthesis by activating adenosine monophosphate-activated protein kinase (AMPK), consequently inhibiting both pathways [22]. It has been shown that gluconeogenesis inhibition is mediated by metformin's ability to suppress mitochondrial glycerol 3- phosphate dehydrogenase (mG3PDH), leading to increased NADH levels. This mechanism is thought to contribute to the life-threatening complication of metformin, lactic acidosis, caused by depletion of NAD+, and the resultant inability to convert lactate to pyruvate [23]. In addition, it has been suggested that metformin increases glucose sensitivity in skeletal muscle by translocation of glucose transporter-4 to the cell membrane, contributing to reduced insulin resistance [24]. Furthermore, metformin inhibits glycogenolysis final step of glycogen breakdown, through the suppression of glucose-6-phosphatase [25].

Aim of the current study

Given the widespread use of metformin over the past decades, and in light of its obscure mechanisms of action, we aimed to investigate the potential association between prior exposure to metformin and the development of a common and devastating malignancy in the elderlies – MDS. Our hypothesis was that an association between past Metformin exposure and subsequent MDS would appear, eve though causality could not be inferred from the results of a retrospective, cross-sectional study.

Methods

Patient population

This cross-sectional study aimed to explore the association between prior use of metformin in patients with Diabetes Mellitus (DM) and the subsequent development of Myelodysplastic Syndrome (MDS). The study was carried out by extracting data from electronic medical records (EMRs) of patients hospitalized at the Chaim Sheba medical center, Israel's largest tertiary medical facility, ensuring a comprehensive analysis of the patient population. All patients were, at some point in time, hospitalized for variable reasons, not necessarily due to MDS or DM complications. The study was approved by the Institutional Review Board (approval # SMC-0540-23) with waving of informed consent due to its retrospective nature.

The study included a total of 54,869 patients with DM, identified through a retrospective review of EMRs. Patients were classified into two groups based on their prior exposure to metformin: those who had received metformin at any time ("metformin group", 20,318 patients) and those with no history of metformin use ("non-metformin group", 34,551 patients).

Variables

Data on DM patient demographics, metformin exposure, and MDS diagnosis were extracted from the EMRs of patients aged 18 and 103 who were hospitalized between January 2007 and August 2024. The primary outcome of this retrospective study was the diagnosis of MDS, identified through diagnostic codes following the patient's first hospitalization at the Chaim Sheba medical center in Israel. Demographic and clinical data collected included gender, age at first hospitalization, and comorbidities such as congestive heart failure (CHF), hypertension, chronic kidney failure (CKD), and dementia. Finally, we included a variable for metformin exposure, differentiating between patients who used any form of metformin and those with no record of such use. The metformin exposure variable was obtained from pharmacy records within the EMR system.

Data analysis

The initial phase of our analysis involved collecting data on hospitalized patients across all departments, focusing on their exposure to metformin and categorizing them into MDS and non-MDS groups. We described normally distributed, continuous variables using means and standard deviations, while non-normally distributed variables were described using medians and interquartile ranges (IQR). To differentiate between normal and non-normal distributions, we used QQ-plot when indicated and applied statistical tests accordingly. For normally distributed variables, we used the student's t-test, while the Mann-Whitney U test was applied for non-normally distributed data. An odds ratio (OR) analysis was used to assess the potential association between prior metformin use and the incidence of MDS. A multivariate analysis was then performed to determine the independent OR of past metformin use, along with other patients characteristics associated with MDS development in the univariate model (e.g., age). All statistical analyses were conducted using R-studio software (version 4.3.0) from the R Foundation for Statistical Computing. Statistical significance was defined as a P-value of less than 0.05.

Results

Among the 54,869 DM patients in the study, a total of 20,318 (37.0%) patients were exposed to metformin at some point in time, and 133 (0.7%) of them developed MDS. In contrast, of the 34,551 patients (63% of the total study cohort), who had no prior exposure to metformin, only 154 (0.4%) developed MDS (a CONSORT flow diagram of patients distribution is presented in Fig. 1).

Demographic and clinical characteristics of the study cohort, including a comparison between the metformin group and the non-metformin group, are shown in Table 1.

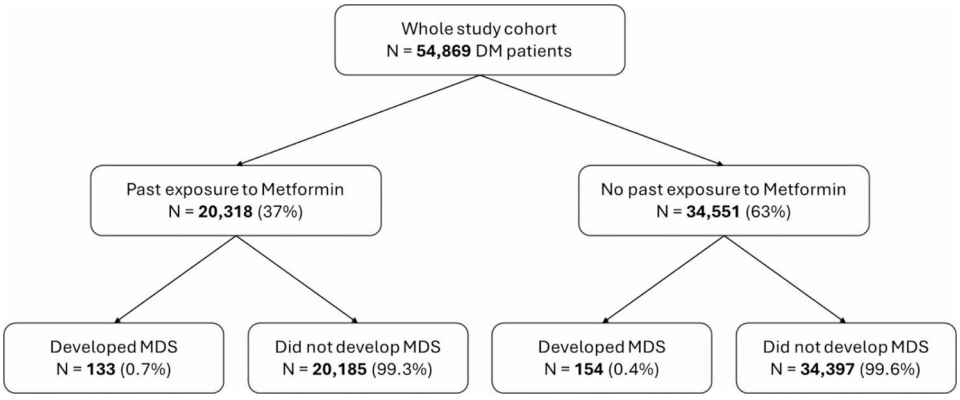

Fig. 1 CONSORT flow diagram

Table 1 Study cohort characteristics according to past Metformin usage

Variable	All patients [*n* = 54,869]	non-Metformin [*n* = 34,551]	Metformin [*n* = 20,318]	*P*-value
Male gender; N (%)	32,747 (59.7)	21,061 (61)	11,686 (57.5)	< 0.001
Age*; years (median [IQR])	71 [62, 79]	71 [62, 79]	70 [62, 78]	< 0.001
MDS; N (%)	287 (0.5)	154 (0.4)	133 (0.7)	0.001
CHF; N (%)	9,837 (17.9)	6,338 (18.3)	3,499 (17.2)	0.001
CKD; N (%)	3,428 (6.2)	3,074 (8.9)	354 (1.7)	< 0.001
Dementia; N (%)	2,114 (3.9)	1,496 (4.3)	618 (3)	< 0.001
Hypertension; N (%)	33,162 (60.4)	21,260 (61.5)	11,902 (58.6)	< 0.001

MDS = myelodysplastic syndrome; CHF = congestive heart failure; CKD = chronic kidney disease

*Age at first hospitalization

A total of 287 patients were diagnosed with MDS at some point after their first hospitalization, with 133 having a history of exposure to metformin and 154 without. MDS occurrence was significantly higher in the group exposed to metformin compared to the group that was not (0.7% vs. 0.4% respectively; $p = 0.001$). There were significantly fewer males in the metformin group, compared to the non-metformin group (57.5% compared to 61% respectively; $p < 0.001$). Additionally, patients in the metformin group were significantly younger than the patients in the non-metformin group (median age of 70 [IQR = 62–78] years compared to 71 [62–79] years, respectively; $p < 0.001$), although the difference between median ages was only one-year. Comorbidities were less prevalent in the metformin group compared to the non-metformin group, including CHF (17.2% vs. 18.3 respectively; $p = 0.001$), CDK (1.7% vs. 8.9% respectively; $p < 0.001$), dementia (3% vs. 4.3% respectively; $p < 0.001$), and hypertension (58.6% vs. 61.5% respectively; $p < 0.001$).

Table 2 Univariate and multivariate analyses

Variable	OR	[95%CI]	*P*-value
Univariate analysis			
Metformin	1.48	[1.17, 1.86]	0.001
Multivariate analysis			
Metformin	1.58	[1.25, 2.01]	< 0.001
Male gender	1.39	[1.08, 1.78]	0.01
Age; one year increment	1.03	[1.02, 1.05]	< 0.001
CHF	1.31	[0.98, 1.71]	0.058
CKD	1.55	[1.01, 2.29]	0.036
Dementia	0.59	[0.28, 1.09]	0.123
Hypertension	0.7	[0.55, 0.88]	0.003

CHF = congestive heart failure; CKD = chronic kidney disease

*Age at first hospitalization

In the univariate logistic regression analysis (Table 1), where MDS was defined as the dependent variable, metformin use was associated with a 48% increased risk of developing MDS (OR = 1.48, 95% CI 1.17–1.86; $p = 0.001$). This association between metformin and MDS strengthened, both in magnitude of the increased risk and in statistical significance, after adjusting for potential confounding variables in the multivariate logistic regression analysis (as also presented in Table 2: OR = 1.58, 95% CI 1.25–2.01; $p < 0.001$). Furthermore, male gender and age at first hospitalization were identified as risk factors for MDS, increasing the risk of MDS by 39% (OR = 1.39, 95% CI 1.08–1.78; $p = 0.01$), and each additional year of age raised the risk by 3% (OR = 1.03, 95%CI 1.02–1.05]; $p < 0.001$). CKD was also a significant predictor of increased MDS risk (OR = 1.55, 95% CI 1.01–2.29]; $p = 0.036$), while hypertension had a protective effect (OR = 0.7, 95% CI 0.55–0.88]; $p = 0.003$). CHF and dementia did not reach statistical significance (OR = 1.31, 95% CI [0.98–1.71]; $p = 0.058$, and OR = 0.59, 95% CI [0.28–1.09]; $p = 0.123$ respectively). Similarly, while CHF and CKD were associated with an increased risk for MDS, these relationships did not reach statistical significance (OR = 1.28, 95% CI [0.97–1.68]; $p = 0.075$, and OR = 1.48, 95% CI [0.97–2.19]; $p = 0.057$ respectively).

Discussion

The co-occurrence of chronic diseases in the elderly population often prompts the question of whether these conditions share common etiologies, or whether one disease, or its therapy, contributes to the development of another. In their health and retirement study, Lee, Cigolle and Blaum [1], surveyed 11,113 adults over the age of 65 years. They found that 23% had at least two of the most common diseases and geriatric syndromes, such as coronary artery disease, congestive heart failure, diabetes mellitus, urinary incontinence, and falls. Therefore, the occurrence of each condition should be investigated for potential causal relationships with other life-threatening diseases commonly seen in older age.

As mentioned earlier, metformin is a widely used medication for managing DM. However, despite its therapeutic advantages, it is associated with a wide range of adverse effects, including lactic acidosis [26], vitamin B12 deficiency anemia [27], hypoglycemic episodes, particularly when combined with dehydration or vigorous physical activity [28], and gastrointestinal disturbances such as diarrhea, which are especially problematic for elderly patients. A case-control study involving over 7,000 patients identified a higher incidence of dementia among metformin users compared to those treated with alternative antidiabetic agents [29]. On the other hand, several studies have reported potential oncological benefits of metformin, suggesting improved survival in patients with cancers such as melanoma, through inhibiting SMAD3 acetylation and TRIB3 expression [30], as well as in colorectal [31], and endometrial cancer [32].

However, the association between metformin use and MDS development in haemato-oncology patients has not been thoroughly investigated. The prevalence of MDS among patients exposed to metformin at their initial diagnosis has been anecdotal, with frequent reports of such cases across different departments at Sheba Medical Center.

The etiology of MDS remains largely unknown, with no definitive causative factors identified. While genetic aberrations are recognized as underlying contributing factors, their origins are unclear. Some hypotheses suggest that earlier environmental exposures might play a role [33]. Additionally, recent research by Feng et al. has highlighted a potential correlation between specific gut microbiota and the incidence of MDS, possibly through effects on immune cell function [34]. However, these findings are not sufficiently specific to establish a direct causal relationship. The lack of a clear etiological factor or proven pathophysiological mechanism, combined with the need to identify effective interventions for MDS patients, prompted this investigation.

Our study evaluated the incidence of MDS in diabetic patients with prior exposure to metformin. Among a cohort of 54,869 diabetic patients, those treated with metformin had a 1.75-fold higher incidence of MDS compared to those who were not. This association was statistically significant and remained robust even after adjusting for other potential confounding factors. Notably, the impact of metformin use on MDS incidence appeared to be greater than that of other known risk factors.

Historically, metformin has been recognized as a drug with a broad side-effect profile, and its use was briefly discontinued in the USA due to safety concerns, only to be reintroduced later [35]. The drug's continued use is likely connected to its long-standing presence in the market over 100 years and its efficacy in managing diabetes. However, under current pharmacovigilance standards, metformin might not meet the strict safety requirements necessary for market approval today, given the need for medications to demonstrate both therapeutic efficacy and a high safety threshold.

A recent case-control study in Denmark suggested that metformin may reduce the incidence of certain myeloproliferative diseases, indicating its potential as a chemo preventive agent [36]. However, the association between metformin uses and the development of MDS, as described in our study, has not been previously investigated. Further research is needed to establish a more definitive understanding of the link between metformin and MDS, and to identify other mechanisms contributing to this devastating manifestation.

Conclusions

In conclusion, our study demonstrates a significant association between prior metformin exposure and an increased risk of developing MDS in patients with DM. Importantly, metformin was identified as an independent risk factor for MDS, even after adjusting for key variables such as age, gender and relevant comorbidities. This does not infer a causal association that should be further investigated. These findings highlight the need for further research to investigate the long-term effect of metformin use, and to establish this important association / causal relationship with MDS development.

Limitations

This was a retrospective, cross-sectional study and as such, both advantages and disadvantages must be acknowledged. Along side its inherent advantages (relatively quick and simple to practice, taking a snapshot of a relevant population, providing the prevalence of and easy identification of trends and patterns, valuable for assessing the burden of disease without a need for longitudinal follow-up) its disadvantages are also significant: A). No Causality should be inferred, B). There is a temporal ambiguity regarding the exact timing of exposure relating

to the outcome, C). There is a potential for Bias: with susceptibility for selection bias, and D). It does not account for changes over a time axis, therefore, making it harder for understanding and explaining certain clinical phenomena [37, 38].

Abbreviations

MDS	Myelodysplastic syndrome
AML	Acute myeloid leukemia
CKD	Chronic kidney disease
CHF	Congestive heart failure
DM	Diabetes mellitus
ICC	International Consensus Classification
IPSS	International Prognostic Scoring System
WHO	World health organization
OR	Odds ratio
CI	Confidence interval

Acknowledgements
N/A.

Author contributions
Tamer Hellou, Guy Dumanis, Shir Portugez, Aviv Philip Goncharov, Eden Trodler, Asaf Stern, Imanuel Carlebach, Omer Kahlon, Maysan Abu Jwella, Ekram Nimer, Ahlam Athamna, Aya Berman, Gad Segal, Reut Kassif Lerner – all participated in conceptualization, data curation and data analysis. All authors contributed to the writing of the original draft and approved the final manuscript.

Funding
This study had no external funding or other resources to declare.

Data availability
Data is provided within the manuscript. Further data is available with the PI according to the IRB specifications.

Declaration

Ethical approval
This study was approved by the Chaim Sheba Institutional Review Board prior to data mining (approval # SMC-0540-23). All methods were carried out in accordance with relevant guidelines and regulations. The study protocol was approved by the Chaim Sheba Institutional Review Board.

Consent to participate
Informed consent was waived by the institutional IRB due to the retrospective nature of this study.

Consent for publication
All authors gave their consent for publication.

Competing interests
The authors declare no competing interests.

Author details
[1]Hematology Division, Chaim Sheba Medical Center, Ramat Gan, Israel
[2]Faculty of Health Science and Medicine, Tel-Aviv University, Tel-Aviv, Israel
[3]Adelson School of Medicine, Ariel University, Ariel 4070000, Israel
[4]Silesia Medical University, Katowice, Poland
[5]Faculty of Medicine and Dentistry, Palacký University in Olomouc, Olomouc 77900, Czech Republic
[6]Faculty of Medicine, Kharkiv National Medical University, Kharkiv, Ukraine
[7]Internal Medicine Division, Sheba Medical Center, Ramat Gan, Israel
[8]Dan Petah-Tikvah District at Clalit Health Service, Petah-Tikvah, Israel
[9]Education Authority, Chaim Sheba Medical Center, Tel-Hashomer, Ramat Gan, Israel
[10]Department of Pediatric Intensive Care, The Edmond and Lily Safra Children's Hospital, at Chaim Sheba Medical Center, Tel Hashomer, Ramat Gan, Israel

Received: 14 December 2024 / Accepted: 25 February 2025
Published online: 27 February 2025

References

1. Lee PG, Cigolle C, Blaum C. The Co-Occurrence of chronic diseases and geriatric syndromes: the health and retirement study. J Am Geriatr Soc. 2009;57:511–6. https://doi.org/10.1111/J.1532-5415.2008.02150.X.
2. Garcia-Manero G, Chien KS, Montalban-Bravo G, Myelodysplastic S. 2021 Update on diagnosis, risk stratification and management. Am J Hematol. 2020;95:1399–420. https://doi.org/10.1002/AJH.25950.
3. Ogawa S, Genetics of MDS. Blood. 2019;133:1049–59. https://doi.org/10.1182/BLOOD-2018-10-844621.
4. Visconte V, Tiu RV, Rogers HJ. Pathogenesis of myelodysplastic syndromes: an overview of molecular and Non-Molecular aspects of the disease. Blood Res. 2014;49:216–27. https://doi.org/10.5045/BR.2014.49.4.216.
5. Oliva EN, Platzbecker U, Fenaux P, Garcia-Manero G, LeBlanc TW, Patel BJ, Kubasch AS, Sekeres MA. Targeting Health-Related quality of life in patients with myelodysplastic Syndromes - Current knowledge and lessons to be learned. Blood Rev. 2021;50:100851–100851. https://doi.org/10.1016/J.BLRE.2021.100851.
6. Kubasch AS, Platzbecker U. Patient stratification in myelodysplastic syndromes: how a puzzle May become a map. Hematology: Am Soc Hematol Educ Program 2020;2020:418. https://doi.org/10.1182/HEMATOLOGY.2020000126.
7. Samiev D, Bhatt VR, Armitage JD, Maness LJ, Akhtari MA. Primary care approach to myelodysplastic syndromes. Korean J Fam Med. 2014;35:111–8. https://doi.org/10.4082/KJFM.2014.35.3.111.
8. Bryan J, Jabbour E, Prescott H, Kantarjian H. Thrombocytopenia in patients with myelodysplastic syndromes. Semin Hematol. 2010;47:274. https://doi.org/10.1053/J.SEMINHEMATOL.2010.02.006.
9. Kota V, Ogbonnaya A, Farrelly E, Schroader BK, Raju A, Kristo F, Dalal M. Clinical impact of transformation to acute myeloid leukemia in patients with Higher-Risk myelodysplastic syndromes. Future Oncol. 2022;18:4017–29. https://doi.org/10.2217/FON-2022-0334/ASSET/IMAGES/LARGE/FIGURE3.JPEG.
10. Shafrin J, Green S, Murphy R, Everson K, Dennen S, Price K, Batt K. Quantifying the economic burden of myelodysplastic syndromes among elderly US patients. Blood. 2019;134:2151–2151. https://doi.org/10.1182/blood-2019-124216.
11. Kaplan H, Malmgren J, De Roos AJ. Risk of myelodysplastic syndrome and acute myeloid leukemia post radiation treatment for breast cancer: A Population-Based study. Breast Cancer Res Treat. 2013;137:863–7. https://doi.org/10.1007/S10549-012-2386-9.
12. Yarosh R, Roesler MA, Murray T, Cioc A, Hirsch B, Nguyen P, Warlick E, Poynter JN. Risk factors for de Novo and therapy related myelodysplastic syndromes (MDS). Cancer Causes Control. 2021;32:241. https://doi.org/10.1007/S10552-020-01378-X.
13. Le Deley MC, Suzan F, Cutuli B, Delaloge S, Shamsaldin A, Linassier C, Clisant S, De Vathaire F, Fenaux P, Hill C, Anthracyclines. Mitoxantrone, radiotherapy, and granulocyte Colony-Stimulating factor: risk factors for leukemia and myelodysplastic syndrome after breast Cancer. J Clin Oncol. 2007;25:292–300. https://doi.org/10.1200/JCO.2006.05.9048.
14. Maung SW, Burke C, Hayde J, Walshe J, McDermott R, Desmond R, McHugh J, Enright H. A review of Therapy-Related myelodysplastic syndromes and acute myeloid leukaemia (t-MDS/AML) in Irish patients: A single centre experience. Hematology. 2017;22:341–6. https://doi.org/10.1080/10245332.2017.1286539.
15. Abou Zahr A, Kavi AM, Mukherjee S, Zeidan AM. Therapy-Related myelodysplastic syndromes, or are they?? Blood Rev. 2017;31:119–28. https://doi.org/10.1016/J.BLRE.2016.11.002.
16. Sun LM, Lin CL, Lin MC, Liang JA, Kao CH. Radiotherapy- and Chemotherapy-Induced myelodysplasia syndrome: A nationwide Population-Based nested Case–Control study. Medicine. 2015;94:e737. https://doi.org/10.1097/MD.0000000000000737.
17. Sweeney MR, Applebaum KM, Arem H, Braffett BH, Poynter JN, Robien K. Medical conditions and modifiable risk factors for myelodysplastic syndrome: A systematic review. Cancer Epidemiol Biomarkers Prev. 2019;28:1502–17. htt

ps://doi.org/10.1158/1055-9965.EPI-19-0106/69651/AM/MEDICAL-CONDITIONS-AND-MODIFIABLE-RISK-FACTORS-FOR.
18. Nisse C, Haguenoer JM, Grandbastien B, Preudhomme C, Fontaine B, Brillet JM, Lejeune R, Fenaux P. Occupational and environmental risk factors of the myelodysplastic syndromes in the North of France. Br J Haematol. 2001;112:927–35. https://doi.org/10.1046/J.1365-2141.2001.02645.X.
19. Bailey CJ, Metformin. Hist Overv Diabetologia. 2017;60:1566–76.
20. Bailey CJ, Day C, Metformin. Its botanical background. Practical Diabetes Int. 2004;21:115–7. https://doi.org/10.1002/pdi.606.
21. Feldman H, ElSayed NA, McCoy RG, Moverley J, Oser SM, Segal AR, Trujillo J, Jones CW, Pilla SJ, Aung NL, et al. Standards of care in Diabetes—2023 abridged for primary care providers. Clin Diabetes. 2023;41:4–31. https://doi.org/10.2337/CD23-AS01.
22. Kaneto H, Kimura T, Obata A, Shimoda M, Kaku K. Multifaceted mechanisms of action of Metformin which have been unraveled one after another in the long history. Int J Mol Sci. 2021;22:1–13.
23. An H, He L. Current Understanding of Metformin effect on the control of hyperglycemia in diabetes. J Endocrinol. 2016;228:R97–106.
24. Hundal HS, Ramlal T, Reyes R, Leiter LA, Klip A. Cellular mechanism of Metformin action involves glucose transporter translocation from an intracellular pool to the plasma membrane in L6 muscle cells. Endocrinology. 1992;131:1165–73. https://doi.org/10.1210/ENDO.131.3.1505458.
25. Wiernsperger N.F., Bailey C.J. The antihyperglycaemic effect of metformin: therapeutic and cellular mechanisms. Drugs. 1999;58(Suppl 1):31–9. https://doi.org/10.2165/00003495-199958001-00009.
26. Lalau JD, Kajbaf F, Protti A, Christensen MM, De Broe ME, Wiernsperger N. Metformin-Associated lactic acidosis (MALA): moving towards a new paradigm. Diabetes Obes Metab. 2017;19:1502–12. https://doi.org/10.1111/DOM.12974.
27. Ahmed MA. Metformin and vitamin B12 deficiency: where do we stand?? J Pharm Pharm Sci. 2016;19:382–98. https://doi.org/10.18433/J3PK7P.
28. Dziubak A, Wójcicka G, Wojtak A, Bełtowski J. Metabolic effects of Metformin in the failing heart. Int J Mol Sci. 2018;19. https://doi.org/10.3390/IJMS19102869.
29. Imfeld P, Bodmer M, Jick SS, Meier CR, Metformin. Other antidiabetic drugs, and risk of Alzheimer's disease: A Population-Based Case-Control study. J Am Geriatr Soc. 2012;60:916–21. https://doi.org/10.1111/J.1532-5415.2012.03916.X.
30. Li K, Zhang TT, Wang F, Cui B, Zhao CX, Yu JJ, Lv XX, Zhang XW, Yang ZN, Huang B, et al. Metformin Suppresses Melanoma Progression by Inhibiting KAT5-Mediated SMAD3 Acetylation, Transcriptional Activity and TRIB3 Expression. Oncogene. 2018;37:2967–2981. https://doi.org/10.1038/s41388-018-0172-9
31. McCreight LJ, Bailey CJ, Pearson ER. Metformin and the Gastrointestinal tract. Diabetologia. 2016;59:426–35. https://doi.org/10.1007/S00125-015-3844-9.
32. Ko EM, Walter P, Jackson A, Clark L, Franasiak J, Bolac C, Havrilesky LJ, Secord AA, Moore DT, Gehrig PA, et al. Metformin is associated with improved survival in endometrial Cancer. Gynecol Oncol. 2014;132:438–42. https://doi.org/10.1016/J.YGYNO.2013.11.021.
33. Anwar N, Arshad A, Fatima N, Shaheen S, Bukhari S, Shamsi T. Environmental and occupational determinants of myelodysplastic syndrome: A Case–Control study from Pakistan. Cancer Rep. 2022;5:e1580. https://doi.org/10.1002/CNR2.1580.
34. Feng Z, Liao M, Guo X, Li L, Zhang L. Effects of immune cells in mediating the relationship between gut microbiota and myelodysplastic syndrome: A bidirectional Two-Sample, Two-Step Mendelian randomization study. Discover Oncol. 2024;15:1–11. https://doi.org/10.1007/S12672-024-01061-6/TABLES/1.
35. Flory J, Lipska K. Metformin in 2019. JAMA. 2019;321:1926–7. https://doi.org/10.1001/JAMA.2019.3805.
36. Kristensen DT, Øvlisen AK, Jakobsen LH, Severinsen MT, Hannig LH, Starklint J, Hilsøe MH, Vallentin AP, Brabrand M, Hasselbalch HC, et al. Metformin use and risk of myeloproliferative neoplasms: A Danish population-based case-control study. Blood Adv. 2024;8. https://doi.org/10.1182/BLOODADVANCES.2023012266.
37. Bangdiwala SI, Basic Epidemiology Research Designs I. Cross-Sectional design. Int J Inj Contr Saf Promot. 2019;26:124–6. https://doi.org/10.1080/17457300.2018.1556415/ASSET//CMS/ASSET/49B60D9A-DBE3-422C-AE3F-D3B3CB228A8A/17457300.2018.1556415.FP.PNG.
38. Asiamah N, Mends-Brew E, Boison BKT. A spotlight on Cross-Sectional research: addressing the issues of confounding and adjustment. Int J Healthc Manag. 2021;14:183–96. https://doi.org/10.1080/20479700.2019.1621022.

Publisher's note