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RESEARCH ARTICLE

Epidemiology and Clinical Advancements in Managing and Treating Diabetes Mellitus

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ABSTRACT

Type 2 diabetes (T2D) is a highly prevalent metabolic disorder which manifests as a result of numerous genetic, epigenetic and life-style factors. According to the estimates of the World Health Organization, about 90% of diabetic patients suffer from T2D. It can be managed by appropriate medication (oral medications and/or insulin) and lifestyle changes including low carbohydrate diet and regular exercise. Mounting evidence suggests that T2D is associated with increased risk of certain cancer including liver, breast, colorectal, pancreatic, endometrial and bladder. However, evidence for the connection between T2D and other cancers such as esophageal cancer and kidney cancer is relatively less conclusive. While the molecular mechanisms linking T2D and cancer are incompletely understood, anti-diabetic drugs are known to have differential effects in cancer patients with T2D. For example, insulin promotes cell proliferation and emergence of chemoresistant whereas metformin suppresses tumor growth. Therefore, an in-depth understanding of molecular factors that link T2D with cancer is crucial for selecting an appropriate anti-hyperglycemic medication for cancer patients suffering from T2D. The current review highlights the potential molecular interactions which play a critical role in metabolic alterations in cancer patients with T2D as well as possible therapeutic strategies that may significantly contribute to the successful management of cancer in patients with diabetic complications.

INTRODUCTION

About 537 million people worldwide have diabetes, making up about 10.5% of the world's population, according to the International Diabetes Federation's 2021 report. Nearly half of all diabetics do not know they have the disease, and low and middle-income countries (LMICs) in Southeast Asia, the Western Pacific, and Africa have the highest rates of undiagnosed diabetes mellitus [1].

Prevalence

Nearly half of all adults with diabetes are unaware that they have the disease, and an estimated 240 million people worldwide live with undiagnosed diabetes. Globally, diabetes places a significant financial burden on healthcare systems. Globally, 537 million people (10.5%) between the ages of 20 and 79 are thought to be managing illness at the moment. According to estimates from the International Diabetes Federation (IDF), 537 million people worldwide—or 10.5% of the total population—had diabetes in 2021, which led to $966 billion in global healthcare costs [2]. By 2045, this health expense is expected to increase to over $1054 billion. The prediction that the number of people with diabetes mellitus will rise to 643 million (11.3%) by 2030 and 783 million (12.2%) by

2045 is concerning. The number of people with diabetes worldwide, measured in millions, is on the rise. The ten countries with the highest rates of diabetes worldwide are Bangladesh, Brazil, Italy, Japan, Indonesia, India, China, the United States, and Russia. As a result, this health issue has become a global emergency. The prevalence of diabetes mellitus is increasing at a significantly faster rate in low- and middle-income countries (LMICs) than in high-income countries. It is important to remember that the majority of diabetics worldwide—nearly 80% of the total population—live in LMICs. It is predicted that 643 million people worldwide will have diabetes by 2030, primarily as a result of a 150% rise in emerging economies [3-5].

In 2021, North Africa and the Middle East experienced consecutive outbreaks of diabetes mellitus (DM) at a rate of 39.4%, with Qatar appearing to be the most affected nation at 76.1%. Africa is expected to see the largest increase in the number of people with diabetes by 2045, with a startling rise of 129%, or about 55 million cases, even though its prevalence estimate is the lowest among IDF Regions at 4.5% [6]. It's interesting to note that, at 53.6%, Africa has the highest percentage of undiagnosed diabetes cases. It's important to note that the African Region only spent 12.6 billion USD on diabetes-related costs, which accounts for 1.3% of all diabetes-related spending worldwide. However, since approximately 4.5% of the world's population has diabetes, this appropriation is out of line with demographic reality. LMICs face a number of socioeconomic issues, including inadequate nutrition, poverty, and a lack of physical activity. A recent report states that accurate, focused data is desperately needed to support the creation of successful programs meant to address these issues [7]. Furthermore, accurately identifying and categorizing the populations most at risk was essential.

Cancer induced diabetes

Cancer and type 2 diabetes (T2D) are two of the most common and prevalent diseases claiming the life of over 10 million people each year. Globally, cancer ranks 2nd while diabetes 12th as a cause of the death [8]. Recently, some epidemiological evidence has indicated that there are various levels of linking to diabetes and cancer significantly. These reports suggest that there are significant chances of cancer and diabetes to be found in the same individuals even after adjusting the age. Both the clinical problems get complicated by their various types, stages and versions whose pathophysiology and prognosis are still not fully understood. Moreover, the individual suffering from chronic T2D are at the higher risk of certain types of cancer including colorectal cancer, pancreatic cancer, liver cancer, endometrium cancer and breast cancer [9]. However, other types of cancer (colon, rectum, and bladder) are less likely to occur in the diabetic individuals while the association in case of kidney cancer and non-Hodgkin lymphoma is still unestablished [10]. Alternatively, it is also reported that the diabetic patients who get cancer have worse prognosis post chemotherapy or surgery with a high mortality rate as compared to those without diabetes [11]. It is also noteworthy that few researchers believe that the pathogenesis of cancer and diabetes involves vitamin D deficiency [12].

The link between both the diseases drew paramount attention when a famous anti-diabetic drug named metformin was found to have antineoplastic activity in an animal model as well as cell lines based studies by many contemporary investigators [13,14]. With accumulation of greater volume of evidence, American Diabetic Association (ADA) and American Cancer Society (ACS) issued a consensus report in December 2009 [15] regarding

i) reviewing of scientific knowledge on the association between diabetes and cancer

ii) exploring the common risk factors for both the diseases

iii) examining the possible biological link

iv) determination of the influence of diabetic treatment on cancer risk or its prognosis

Hence, nowadays, a section of researchers are focused on finding out the common thread of both diseases so that both the diseases could be managed and contained for maximum clinical benefits [16].

It is well established that diabetic patients because of malfunctioning or dysfunction of pancreatic beta-cells have an abundance of glucose in the cells while cancer cells survive and thrive on glucose as the main nutrient besides glutamine. The thread of pathogenesis and progression of both the diseases lies in an alteration in glucose metabolizing pathways. On one hand, T2D patients have elevated the level of blood glucose because of defects in insulin secretion, action as well as a response in the target tissues. Besides, many patients develop insulin resistance (IR). It is considered as an early pathogenic sign of T2D in which efficacy of the hormone declines significantly leading to failure of pancreatic beta-cell accompanied by hyperglycemia as the major consequence [17]. Obesity-driven T2D patients, accumulation of excess lipid/fats in visceral organs like liver, kidney and muscles leads to IR accompanied by disturbed glucose and fatty acid homeostasis. Moreover, the T2D individuals have chronic low-grade inflammation sustained by local and systemic oxidative stress in target organs including white adipose tissues where an alteration in metabolic energetics give rise to numerous reactive oxygen species (ROS). These changes ultimately impair insulin sensitivity exacerbating the disease further [18].

On the other hand, cancer arises from genetic mutations that enable cancer cells to proliferate uncontrollably evading cell death. It has been reported earlier that cancer cells adapt and thrive on aerobic glycolysis concomitant with restricted mitochondrial oxidative phosphorylation. Further studies reveal that cancer cells adopt a marked metabolic alteration that facilitate tumor cells to use all nutrients in fulfilling excessive cell division and biosynthesis of macromolecules [19]. It is also well established that glucose and glutamine are the two most important fuel molecules for cancer cells that provide all the favorable energetics as well as their metabolic intermediates acting for maintenance and sustenance of tumorigenesis. Moreover, glutamine in tumor cells is used as the alternate feeder molecule to compensate TCA cycle intermediates for oxidative phosphorylation in mitochondria [20]. Hence, cancer cells are genetically redesigned (after mutations at the target genes including proto-oncogenes and tumor suppressor genes) to force a metabolic shift that enable them to coordinate aerobic glycolysis, glutamine uptake, and cellular biosynthesis. These facilitate continuous tumor growth and their metastasis evading from normal cell cycle signaling molecules). Also, tumor hypoxia is a contributing metabolic alteration in tumor cells that stabilize hypoxia-inducible factors 1 and 2 [21,22]. After induction, HIF-1, one hand upregulates rate of glycolysis and blocks entry of pyruvate into TCA cycle; whereas HIF-2 enhances Myc function that accelerate tumor growth in hypoxic condition [23]. A great deal of literature suggests oncogenes and tumor suppressor genes exert an impact on major metabolic pathways and also dictate their alteration in tumor cells that contribute in cellular transformation and tumorigenesis. For example, Myc is an oncogene that have been found mutated in many forms of cancer that activates the expression of LDH [24].

THE COMMON GROUND: DIABETIC PHYSIOLOGICAL CONDITIONS FACILITATE CELLULAR TRANSFORMATION AND TUMORIGENESIS

A lot of the epidemiological reports vividly indicate that many chronic diabetic patients are susceptible to certain types of cancer [25]. The target organs involved in diabetes that are centrally active metabolic organs like the pancreas, liver and kidney further show the greater association in between the diseases although it is yet to be elucidated. Tumor cells have three essential requirements for their proliferation and sustenance: Rapid generation of energy, Enhanced biosynthesis, Suitable redox status. All these conditions are facilitated in a chronic diabetic condition involving intricate metabolic, hormonal and genetic alteration [26].

Role of hyperinsulinemia

The physiological and metabolic changes brought up by diabetes during its pathogenesis and progression facilitate tumorigenesis [27]. With the beginning of the T2D, beta cells of pancreas secrete excessive of insulin leading to the physiological condition as hyperinsulinemia. The target cells respond either scantily or null to the surplus amount of insulin in the diseased condition. Under

such situation, the hormone might exert its effect as a conditional growth factor for the nascent tumors triggering their abrupt growth as tumorigenesis. It is noteworthy to mention that both insulin and IGF-1 have potential mitogenic and anti-apoptotic activities [28]. It has been observed that cancer cells respond positively in the presence of high level of insulin and insulin-like growth factor 1 (IGF-1) by stimulating their proliferation [Fig 1] and promoting glucose consumption in an insulin-dependent subset of tumors [29,30]. Hence, it is highly speculative that high level of insulin if sustained for a longer time can trigger tumorigenesis in the vulnerable nascent tumor cells *in vivo*.

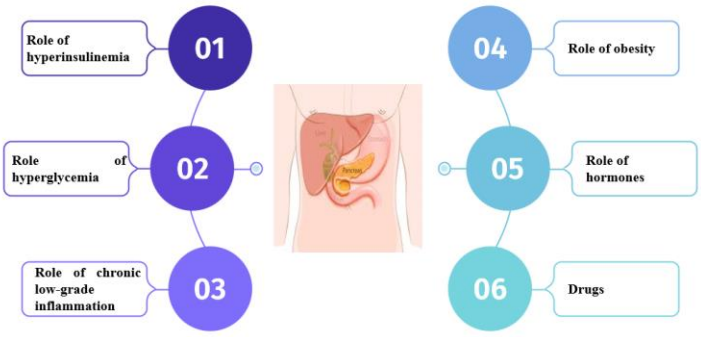

Fig 1: Various physiological and metabolic changes in diabetes facilitating tumorigenesis

Role of hyperglycemia

Glucose being the central fuel molecule for cancer cells, diabetes-induced hyperglycemia also contributes in tumorigenesis in direct and indirect ways. High level of glucose boosts the energy generation machinery inside the target cells like glycolysis and mitochondrial ATP generation concomitant with the surplus generation of reactive oxygen species (ROS). These can force the target cells either to undergo apoptosis/necrosis or might induce mutation in proto-oncogenes and tumor suppressor genes [31,32]. Such observations have been reported in many cell line-based studies including Panc-1 and BxPC-3 in which hyperglycemia-mediated ROS increased cellular motility and invasiveness quite similar to metastatic features [33]. Furthermore, enhanced glucose level enables cancer cells to avoid cytochrome C-mediated programmed cell death and also generates resistance towards antineoplastic agents consequently resulting in the form of continued cell proliferation and metastasis [34,35].

Role of chronic low-grade inflammation

Apart from these, excessive availability of nutrients like glucose, glutamine, and fatty acids enhance the frequency of mitochondrial oxidative phosphorylation and beta-oxidation in an abnormal way in chronic diabetic condition. These metabolic activities beyond certain limit give rise to ROS in excess that leads to chronic low-grade inflammation in the target tissues. Besides, excessive ROS and stimulation of concerned cytokines (TNF-alpha, IL-6) contribute to cellular transformation by the introduction of mutations in tumor suppressor genes and proto-oncogenes in vulnerable and nascent tumorous cells [36-38]. The same set of immunological and related alteration in microenvironment as well as in macroenvironment facilitates angiogenesis and metastasis for the cells. Moreover, ROS and reactive nitrogen species (RNS) after a certain threshold period of inflammation can perturb cellular components, constituent biomolecules and structural integrity that consequently can exacerbate overall immune and metabolic system in the affected individual severing the diseased condition to further [39,40].

Role of obesity

Obese people have high lipid/fat content stored in adipose tissues and visceral portions. It is one of most common features of diabetic people also as their waistline exceeds the ideal limits. In such obese people, adipose tissues can act as an active endocrine organ that can produce free fatty acids

with many of the immunologically active molecules and cytokines including IL-6, monocyte chemoattractant proteins, Plasminogen activator inhibitor (PAI-1), adiponectin, leptin, and TNF-alpha. All of these molecules directly or indirectly orchestrate the macroenvironment for cellular transformation, cancer progression and metastasis [41,42].

Role of hormones

It is established that the main reason of T2D is disturbed insulin homeostasis in the diabetic patients. To compensate this deficit in the patients, the rest of the glands reorganize their activity leading to a hormone-driven metabolic shift in many ways. The T2D conditions accompanied by hyperinsulinemia and hyperglycemia, adipocytes express aromatase enzyme that can synthesize lipid-based hormones- androgen and estrogen [43]. It has been documented that the obese men and postmenopausal women have a higher level of estrogen as compared to the slim individuals [44]. Excessive availability of these hormones might trigger hormone responsive cancers including breast cancer, prostate cancer, and cervical cancer, etc. [45,46].

AVAILABLE TREATMENT STRATEGIES AND MANAGEMENT

The distinguished features of cancer metabolism have been extensively exploited for initial diagnosis, staging disease, monitoring tumor responses to therapies, and detecting cancer recurrence [47]. Therefore, nowadays, metabolic molecular imaging plays an indispensable role in clinical oncology. These diagnostic methods are non-invasive and can accurately detect the changes in selective biologic processes of tumors compared to normal surrounding tissues both at the initial tumor sites and metastatic locations over an extended period. The information provided by advanced imaging modalities such as Positron emission tomography, magnetic resonance spectroscopy imaging, magnetic resonance imaging, is very valuable for cancer detection, prevention, and treatment [48]. The underlying premise of disease management involves the right guidance and proper equipment utilization to the diseased population in a cost-effective manner. Improved glucose control remains one of the central goals of effective diabetes management, which strives to minimize morbidity and mortality by reducing the risk of diabetes-associated complications. Several factors which are considered by clinicians and patients when selecting pharmacologic diabetes therapies includes the glucose-lowering potential of a given agent, known acute and chronic adverse effects of treatment (such as weight gain, hypoglycemia, fluid retention, gastrointestinal intolerance), treatment costs and patient comorbidities and characteristics. Hormone therapy may prove a good strategy for curing these diseases. However, adherence to a diabetic diet is a critical aspect of controlling blood sugar in people with diabetes. It is important to properly manage diabetes during cancer treatment. Cancer and cancer treatment can bring about metabolic changes that cause or aggravate symptoms of diabetes. Also, high blood sugar levels brought on by diabetes can weaken the immune system, which needs to be strong to fight cancer. Likewise, diabetes could potentially delay cancer treatment or increase the risk of infection during treatment [49,50].

CONCLUSIONS AND FUTURE DIRECTIONS

Although the precise mechanisms and pathways are uncertain, it is becoming clear that hyperinsulinemia and possibly sustained hyperglycemia are important regulators of not only the development of cancer but also of treatment outcome. Further, clinical decision-making regarding the treatment of choice for diabetes mellitus will likely be impacted as we learn more about the non-metabolic effects of the available hyperglycemic agents. More concerning is the fact that youth are becoming more and more obese, which in time will yield an adult population with a high prevalence of lifelong obesity and insulin resistance people who are likely to be at the highest risk of obesity-related cancer. It is imperative that we continue to clarify the effects of the metabolic syndrome on cancer, while at the same time striving to reverse the obesity epidemic to help our and future generations.

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CONFLICTS OF INTEREST

The authors state no conflict of interest.

REFRENCES

1. 1.Janić M, Janež A, El-Tanani M, Maggio V, Rizzo M. Diabetes: Recent Advances and Future Perspectives. *Biomedicines*. 2024; 12(12):2875.
2. Alshaikh AA, Al-Qahtani FS, Taresh HMN, Hayaza RAA, Alqhtani SSM, Summan SI, Al Mansour SA, Alsultan OHA, Asiri HYM, Alqahtani YMS, et al. Prediction of Diabetes and Prediabetes among the Saudi Population Using a Non-Invasive Tool (AUSDRISK). *Medicina*. 2024; 60(5):775.
3. Chandrasekaran P, Weiskirchen R. The Role of Obesity in Type 2 Diabetes Mellitus—An Overview. *International Journal of Molecular Sciences*. 2024; 25(3):1882. https://doi.org/10.3390/ijms25031882
4. Ukke GG, Boyle JA, Reja A, Lee WK, Chen M, Ko MSM, Alycia C, Kwon J, Lim S. A Systematic Review and Meta-Analysis of Type 2 Diabetes Prevention Through Lifestyle Interventions in Women with a History of Gestational Diabetes—A Summary of Participant and Intervention Characteristics. *Nutrients*. 2024; 16(24):4413. https://doi.org/10.3390/nu16244413
5. Mokhele S, Mokhele T. Prevalence and Determinants of Household Self-Reported Diabetes Mellitus in Gauteng, South Africa. *International Journal of Environmental Research and Public Health*. 2024; 21(11):1537. https://doi.org/10.3390/ijerph21111537
6. Bergman M, Manco M, Satman I, Chan J, Schmidt MI, Sesti G, Vanessa Fiorentino T, Abdul-Ghani M, Jagannathan R, Kumar Thyparambil Aravindakshan P, Gabriel R, Mohan V, Buysschaert M, Bennakhi A, Pascal Kengne A, Dorcely B, Nilsson PM, Tuomi T, Battelino T, Hussain A, Ceriello A, Tuomilehto J. International Diabetes Federation Position Statement on the 1-hour post-load plasma glucose for the diagnosis of intermediate hyperglycaemia and type 2 diabetes. Diabetes Res Clin Pract. 2024 Mar;209:111589.
7. Bergman M, Abdul-Ghani M, DeFronzo RA, Manco M, Sesti G, Fiorentino TV, Ceriello A, Rhee M, Phillips LS, Chung S, Cravalho C, Jagannathan R, Monnier L, Colette C, Owens D, Bianchi C, Del Prato S, Monteiro MP, Neves JS, Medina JL, Macedo MP, Ribeiro RT, Filipe Raposo J, Dorcely B, Ibrahim N, Buysschaert M. Review of methods for detecting glycemic disorders. Diabetes Res Clin Pract. 2020 Jul;165:108233. doi: 10.1016/j.diabres.2020.108233. Epub 2020 Jun 1. Erratum in: Diabetes Res Clin Pract. 2021 Oct;180:108632.
8. Holt, R.I.G., Cockram, C.S., Ma, R.C.W. Diabetes and infection: review of the epidemiology, mechanisms and principles of treatment. *Diabetologia* **67**, 1168–1180 (2024).
9. Ekwebene, O.C., Mensah, E.A., Ekwebene, C.F. *et al.* Prevalence and predictors of cancer among diabetic individuals in the United States. *Discov Epidemics* **1**, 3 (2024).
10. Tkaczenko, H., Kamiński, P., Kurhaluk, N. (2024). Diabetes Mellitus and the Risk of Carcinogenesis: An Interdisciplinary Approach. In: Interdisciplinary Cancer Research. Springer, Cham. https://doi.org/10.1007/16833_2024_426.
11. Gu, J., Lu, H., Chen, C. Diabetes mellitus as a risk factor for chemotherapy-induced peripheral neuropathy: a meta-analysis. *Support Care Cancer* **29**, 7461–7469 (2021).
12. Hadgu, A., Yan, F. & Mayberry, R. The Association Between Vitamin D Deficiency and Diabetes in Adult African Americans and Whites: An NHANES Study. *J. Racial and Ethnic Health Disparities* (2024).

13. Singh R, Gholipourmalekabadi M, Shafikhani SH. Animal models for type 1 and type 2 diabetes: advantages and limitations. Front Endocrinol (Lausanne). 2024 Feb 20;15:1359685.
14. Hasan MM, Ahmed QU, Mat Soad SZ, Tunna TS. Animal models and natural products to investigate in vivo and in vitro antidiabetic activity. Biomed Pharmacother. 2018 May;101:833-841.
15. Abeysekera KWM, Valenti L, Younossi Z, Dillon JF, Allen AM, Nourredin M, Rinella ME, Tacke F, Francque S, Ginès P, Thiele M, Newsome PN, Guha IN, Eslam M, Schattenberg JM, Alqahtani SA, Arrese M, Berzigotti A, Holleboom AG, Caussy C, Cusi K, Roden M, Hagström H, Wong VW, Mallet V, Castera L, Lazarus JV, Tsochatzis EA. Implementation of a liver health check in people with type 2 diabetes. Lancet Gastroenterol Hepatol. 2024 Jan;9(1):83-91. doi: 10.1016/S2468-1253(23)00270-4.
16. Lu Y, Zhang Q, Wang X, Jiang Y, Xue Y. Usefulness of glucose management indicator derived from continuous glucose monitoring to assess glycemic condition in hospitalized patients with diabetic kidney disease treated with insulin pumps. J Diabetes Complications. 2023 Nov;37(11):108613.
17. Jonas JC, Sharma A, Hasenkamp W, Ilkova H, Patanè G, Laybutt R, Bonner-Weir S, Weir GC. Chronic hyperglycemia triggers loss of pancreatic beta cell differentiation in an animal model of diabetes. J Biol Chem. 1999 May 14;274(20):14112-21.
18. Volpe CMO, Villar-Delfino PH, Dos Anjos PMF, Nogueira-Machado JA. Cellular death, reactive oxygen species (ROS) and diabetic complications. Cell Death Dis. 2018 Jan 25;9(2):119.
19. Marbaniang C, Kma L. Dysregulation of Glucose Metabolism by Oncogenes and Tumor Suppressors in Cancer Cells. Asian Pac J Cancer Prev. 2018 Sep 26;19(9):2377-2390.
20. DeBerardinis RJ, Cheng T. Q's next: the diverse functions of glutamine in metabolism, cell biology and cancer. Oncogene. 2010 Jan 21;29(3):313-24.
21. Catrina SB, Zheng X. Hypoxia and hypoxia-inducible factors in diabetes and its complications. Diabetologia. 2021 Apr;64(4):709-716.
22. Gunton JE. Hypoxia-inducible factors and diabetes. J Clin Invest. 2020 Oct 1;130(10):5063-5073.
23. Dang CV. MYC, metabolism, cell growth, and tumorigenesis. Cold Spring Harb Perspect Med. 2013 Aug 1;3(8):a014217.
24. Musleh Ud Din S, Streit SG, Huynh BT, Hana C, Abraham AN, Hussein A. Therapeutic Targeting of Hypoxia-Inducible Factors in Cancer. Int J Mol Sci. 2024 Feb 8;25(4):2060.
25. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, Pollak M, Regensteiner JG, Yee D. Diabetes and cancer: a consensus report. Diabetes Care. 2010 Jul;33(7):1674-85.
26. Chang, WC., Hsieh, TC., Hsu, WL. Diabetes and further risk of cancer: a nationwide population-based study. *BMC Med* **22**, 214 (2024).
27. Lu, X., Xie, Q., Pan, X. Type 2 diabetes mellitus in adults: pathogenesis, prevention and therapy. *Sig Transduct Target Ther* **9**, 262 (2024).
28. Kasprzak A. Insulin-Like Growth Factor 1 (IGF-1) Signaling in Glucose Metabolism in Colorectal Cancer. *International Journal of Molecular Sciences*. 2021; 22(12):6434.
29. Murphy N, Knuppel A, Papadimitriou N, Martin RM, Tsilidis KK, Smith-Byrne K, Fensom G, Perez-Cornago A, Travis RC, Key TJ, Gunter MJ. Insulin-like growth factor-1, insulin-like growth factor-binding protein-3, and breast cancer risk: observational and Mendelian randomization analyses with ~430 000 women. Ann Oncol. 2020 May;31(5):641-649.
30. Murphy N, Knuppel A, Papadimitriou N, Martin RM, Tsilidis KK, Smith-Byrne K, Fensom G, Perez-Cornago A, Travis RC, Key TJ, Gunter MJ. Insulin-like growth factor-1, insulin-like growth factor-binding protein-3, and breast cancer risk: observational and Mendelian randomization analyses with ~430 000 women. Ann Oncol. 2020 May;31(5):641-649.

31. Waris G, Ahsan H. Reactive oxygen species: role in the development of cancer and various chronic conditions. J Carcinog. 2006 May 11;5:14.
32. Srinivas US, Tan BWQ, Vellayappan BA, Jeyasekharan AD. ROS and the DNA damage response in cancer. Redox Biol. 2019 Jul;25:101084.
33. Aggarwal V, Tuli HS, Varol A, Thakral F, Yerer MB, Sak K, Varol M, Jain A, Khan MA, Sethi G. Role of Reactive Oxygen Species in Cancer Progression: Molecular Mechanisms and Recent Advancements. Biomolecules. 2019 Nov 13;9(11):735.
34. Jiang X, Wang X. Cytochrome C-mediated apoptosis. Annu Rev Biochem. 2004;73:87-106.
35. Shen, S., Shao, Y. & Li, C. Different types of cell death and their shift in shaping disease. *Cell Death Discov.* **9**, 284 (2023).
36. Popko K, Gorska E, Stelmaszczyk-Emmel A, Plywaczewski R, Stoklosa A, Gorecka D, Pyrzak B, Demkow U. Proinflammatory cytokines Il-6 and TNF-α and the development of inflammation in obese subjects. Eur J Med Res. 2010 Nov 4;15 Suppl 2(Suppl 2):120-2.
37. Tylutka A, Walas Ł, Zembron-Lacny A. Level of IL-6, TNF, and IL-1β and age-related diseases: a systematic review and meta-analysis. Front Immunol. 2024 Mar 1;15:1330386.
38. Pantovic-Stefanovic, M., Velimirovic, M., Jurisic, V. Exploring the role of TNF-α, TGF-β, and IL-6 serum levels in categorical and noncategorical models of mood and psychosis. *Sci Rep* **14**, 23117 (2024).
39. Afanas'ev I. Signaling of reactive oxygen and nitrogen species in Diabetes mellitus. Oxid Med Cell Longev. 2010 Nov-Dec;3(6):361-73.
40. Son SM. Reactive oxygen and nitrogen species in pathogenesis of vascular complications of diabetes. Diabetes Metab J. 2012 Jun;36(3):190-8.
41. Yu Y, Li W, Xu L and Wang Y (2023) Circadian rhythm of plasminogen activator inhibitor-1 and cardiovascular complications in type 2 diabetes. Front. Endocrinol. 14:1124353.
42. Yarmolinsky, J., Bordin Barbieri, N., Weinmann, T. *et al.* Plasminogen activator inhibitor-1 and type 2 diabetes: a systematic review and meta-analysis of observational studies. *Sci Rep* **6**, 17714 (2016).
43. Tchernof A, Mansour MF, Pelletier M, Boulet MM, Nadeau M, Luu-The V. Updated survey of the steroid-converting enzymes in human adipose tissues. J Steroid Biochem Mol Biol. 2015 Mar;147:56-69.
44. Zhang J, Yin J, Song X, Lai S, Zhong S, Jia Y. The effect of exogenous estrogen on depressive mood in women: A systematic review and meta-analysis of randomized controlled trials. J Psychiatr Res. 2023 Jun;162:21-29.
45. Hugh JC, Haddon LSJ, Githaka JM. DREAM On, DREAM Off: A Review of the Estrogen Paradox in Luminal A Breast Cancers. *Biomedicines*. 2024; 12(6):1300.
46. Kranjčević J-K, Čonkaš J, Ozretić P. The Role of Estrogen and Estrogen Receptors in Head and Neck Tumors. *Cancers*. 2024; 16(8):1575.
47. Aloke C, Egwu CO, Aja PM, Obasi NA, Chukwu J, Akumadu BO, Ogbu PN, Achilonu I. Current Advances in the Management of Diabetes Mellitus. *Biomedicines*. 2022; 10(10):2436.
48. Elkhalifa AME, Nazar M, Ali SI, Khursheed I, Taifa S, Ahmad Mir M, Shah IH, Malik M, Ramzan Z, Ahad S, et al. Novel Therapeutic Agents for Management of Diabetes Mellitus: A Hope for Drug Designing against Diabetes Mellitus. *Life*. 2024; 14(1):99.
49. Kounatidis D, Vallianou NG, Karampela I, Rebelos E, Kouveletsou M, Dalopoulos V, Koufopoulos P, Diakoumopoulou E, Tentolouris N, Dalamaga M. Anti-Diabetic Therapies and Cancer: From Bench to Bedside. *Biomolecules*. 2024; 14(11):1479.
50. Shouman M, Brabant M, Rehman N, Ahmed S, Shahid RK. Perioperative Management of Patients with Diabetes and Cancer: Challenges and Opportunities. *Cancers*. 2024; 16(16):2821.