Biological Forum – An International Journal **15(10): 571-575(2023)**

ISSN No. (Print): 0975-1130
ISSN No. (Online): 2249-3239

The Relationship between Diabetes Mellitus and Cancer

Mayank Patel*[1], Anamika Pandey [1], Shamshad Ali [1], Preeti Verma [1], Prem Kumar[2] and Vikrant Singh Chouhan[3]

[1] Ph.D. Scholar, Division of Physiology & Climatology,
ICAR-Indian Veterinary Research Institute, Izatnagar, Bareilly (Uttar Pradesh), India.
[2] M. V. Sc. Scholar, Division of Physiology & Climatology,
ICAR-Indian Veterinary Research Institute, Izatnagar, Bareilly (Uttar Pradesh), India.
[3] Senior Scientist, Division of Physiology & Climatology,
ICAR-Indian Veterinary Research Institute, Izatnagar, Bareilly (Uttar Pradesh), India.

(Corresponding author: Mayank Patel)*
(Received: 12 July 2023; Revised: 26 August 2023; Accepted: 22 September 2023; Published: 15 October 2023)
(Published by Research Trend)

ABSTRACT: Diabetes mellitus (DM) and cancer are the two most common chronic diseases that increase concern due to their rising global prevalence. While they are traditionally viewed as distinct medical conditions, emerging research suggests a complex interplay between these two conditions. Diabetes mellitus is characterised by high body blood glucose levels caused by either insufficient production of insulin hormone (Type 1 DM) or insulin hormone resistance (Type 2 DM). On the other hand, cancer is characterized by the uncontrolled growth and spread of abnormal cells. Recent epidemiological study indicate a link between diabetes mellitus and an increased risk of various cancers, including pancreatic, liver, breast and bladder cancer. This suggests that the metabolic and hormonal alteration in diabetes play a significant role in cancer development. Several mechanisms have been proposed to explain the potential link between these two conditions via the PI3K/Akt/mTOR and WNT/beta-catenin signalling pathways. Hyperinsulinemia, hyperglycemia, chronic inflammation and obesity create microenvironments which promote cancer development in diabetic patients. Furthermore, various new cancer therapies, including PI3K inhibitors and immune checkpoint inhibitors unveil underlying diabetes mellitus or aggravate pre-existing diabetes. So, there is a complex link between diabetes mellitus and cancer. Understanding this connection is crucial for developing strategies to reduce the potential risk of diabetes mellitus in individuals with cancer and vice versa.

Keywords: Hyperinsulinemia, Hyperglycemia, Obesity, Glucocorticoids, Immunotherapy.

INTRODUCTION

India has an estimated 77 million people diagnosed with diabetes mellitus, which makes it the second most affected disease in the world, after China (Kannan, 2019). One in six people (17%) in the world with diabetes is from India (Kannan, 2019). The diabetes mellitus cases will reach 134 million by 2045 as per the international diabetes federation. Total cancer cases in India for 2022 are 1,461,427, with breast and lung cancers being the leading sites for females and males, respectively (Sathishkumar *et al.*, 2022).

Diabetes mellitus appears to increase the incidence of cancer cases. On the other hand, several cancers and cancer treatments raise the risk of diabetes mellitus. Cancer and diabetes mellitus appear to be linked by genetic factors, hyperglycemia, obesity, inflammation, oxidative stress, elevated insulin levels, hypoglycemic medications and cancer therapy (Zhu and Qu 2022).

A. Cancer Risk in Diabetes

Hyperglycemia. Epidemiological studies have demonstrated a connection between elevated blood sugar levels (hyperglycemia) and an increased risk of developing pancreatic, liver, gastric, colorectal and lung cancer (Xu *et al.*, 2016). This relationship is partially explained by the "Warburg effect," a phenomenon described by Warburg (1956). In normal cells, energy is primarily produced through mitochondrial oxidative phosphorylation to support biological processes. However, cancer cells tend to favour a less efficient glycolytic pathway for their growth, (Koppenol and Bounds 2009). As a result, cancer cells require higher glucose uptake to generate the necessary energy for their rapid proliferation (Devic, 2016). Diabetes-related cancer risk may be caused by an imbalance in signal transduction pathways that regulate nutrition and fuel utilisation (Pollak, 2008). Elevated blood sugar levels (hyperglycemia) trigger the production of advanced glycation end products (AGEs) within the body. These AGEs commonly bind to their specific receptor known as RAGE, instigating the activation of NF-κB and the generation of reactive oxygen species (ROS) in cells. Therefore, this process accelerates oxidative stress and leads to an increased pro-inflammatory signalling cascade (Abe and Yamagishi 2008). Research has demonstrated that the activation of the AGEs pathway

plays a role in promoting the transformation of epithelial cells into tumours (Sparvero *et al.,* 2009). Furthermore, clinical studies have shown a positive correlation between the interaction of AGEs with RAGE and the risk of developing stomach cancer (Kuniyasu *et al.,* 2002), pancreatic cancer (Takada *et al.,* 2004) and melanoma (Abe and Yamagishi 2008). Hyperglycemia causes the body to produce advanced glycation end products (AGEs). AGEs often interact with their specific receptor, RAGE, activate NF-κB and generate ROS in cells, thereby accelerating oxidative stress that leads to increased pro-inflammatory signaling (Abe and Yamagishi 2008). Activation of the AGEs pathway has been demonstrated to promote tumor transformation of epithelial cells (Sparvero *et al.,* 2009). The AGE/RAGE interaction and risk of stomach cancer were found to be positively correlated in clinical studies (Kuniyasu *et al*., 2002), pancreatic cancer (Takada *et al.,* 2004) and melanoma (Abe and Yamagishi 2008). A previously unknown direct pathway connecting diabetes-associated hyperglycemia to cancer has been identified as high glucose increase of WNT/beta-catenin signalling in cancer cells, which promotes proliferation, survival and senescence bypass (Garcia-Jimenez *et al*., 2014). Additionally, DNA damage, the precursor to cancer, is brought on by hyperglycemia (Calle and Kaaks 2004).

Metformin injection in diabetes has been linked to significantly lower cancer incidence and death, according to a large number of clinical studies and meta-analyses (Soranna *et al*., 2012). Furthermore, the incorporation of metformin has been found to mitigate the increased cancer risk associated with therapeutic use of sulfonylurea or insulin in patients (Currie *et al.,* 2009). These observation suggest that metformin could reduce the growth of cancer were supported by various studies conducted in vivo and in vitro (Heckman-Stoddard *et al*., 2017). The metformin inhibits mTOR lead to increases insulin sensitivity and reduce insulin levels. Moreover, metformin exerts its anticancer activity by regulating various other targets, including p53 and STAT 3. Additionally, there is evidence indicating that metformin enhances the efficacy of numerous cancer drugs, including platinum compounds (Morgillo *et al.,* 2013).

Hyperinsulinemia. Hyperinsulinemia is a condition where the pancreas produces more insulin to compensate insulin resistance in type 2 diabetes mellitus (Thomas *et al*., 2019). According to multiple epidemiological studies, hyperinsulinemia raises the chance of developing various cancers, including endometrial, colon, ovarian, breast, kidney and pancreatic cancers (Stolzenberg-Solomon *et al*., 2005). In fact, research conducted in both in vivo and in vitro conditions indicates that insulin and the insulin receptor were important in the biology of cancer (Frasca *et al*., 2008). Hepatic IGF-1 production increased as a result of growth hormone receptor (GHR) activation and enhanced GHR signalling under hyperinsulinemic conditions. In meta-analyses and epidemiological studies, IGF-1 concentrations have been linked with higher risk of lung, colorectal, prostate and breast cancers (Chen *et al*., 2009). In contrast, IGF-1 gene knockout reduced the tumor's growth (Yakar *et al.,* 2005). Furthermore, IGF-2 overexpression has been linked to the emergence of colon cancer in mice models (Sakatani *et al*., 2005). IGF-1, IGF-2 and insulin activate the PI3K/Akt/mTOR signalling pathway, which leads to development of cancers (Gallagher and LeRoith 2010).

Obesity. It is commonly recognised that the majority of people who have type 2 diabetes mellitus (T2DM) or prediabetes are obese or overweight (Bramante *et al.,* 2017). Calle *et al*. (2003) found a significant increase in mortality from cancers of the pancreas, liver, rectum, colon, kidney, oesophagus and colon among individuals who were severely obese. Obesity may be a significant confounder in the connection between T2DM and cancer (Suh and Kim 2019). Butler *et al*. (2010) explore the effects of diabetes mellitus and obesity on pancreatic ductal pathology. They reported that replication of duct epithelium was four times higher in lean diabetics than the lean non-diabetics, and replication of pancreatic duct epithelium was ten times higher in samples taken from obese non-diabetics than the lean non-diabetics. These findings suggest that diabetes mellitus and obesity have significant effects on developing pancreatic exocrine neoplasia (Butler *et al*., 2010).

Inflammation and Oxidative Stress. Inflammation has an important role in the relationship between diabetes mellitus and cancer (Balkwill and Mantovani 2001). Chronic inflammation, defined by high levels of oxidative stress and reactive oxygen species (ROS), activation of pro-inflammatory pathways and abnormal adipokine production, may create a microenvironment that promotes cancer cell growth, enhances metastasis, increases angiogenesis and impairs natural killer cell function (Lin and Karin 2007). Oxidative stress is also an important factor in the relationship between diabetes mellitus and cancer. Higher blood glucose level could elevate superoxide production (Yu and Yoon 2006). Additionally, insulin could increase ROS production (Aggeli *et al.,* 2011). It has been proven that oxidative stress has a significant impact on a variety of gene expression and signal transduction pathways involved in cancer. ROS has been found to affect cell growth and apoptosis via activating cytokine-dependent NF-κB signalling pathways (Valko *et al.,* 2007).

B. Diabetes Risk in Cancer

Glucocorticoid. Glucocorticoids are a common treatment for blood malignancies (Heidari *et al.,* 2012). They are also used to treat nausea, cachexia, discomfort and vomiting caused by cancer (Paulsen *et al.,* 2013). They also aid in the treatment of inflammatory side effects of cancer treatment and autoimmune illnesses associated with immunomodulatory drugs (Jamil and Mineishi 2015). A prior study indicated that treating individuals with previously well-controlled T1DM with 60 mg prednisone daily for three days resulted in worsening glycemic control despite an average 70% increase in insulin dosage (Bevier *et al.,* 2008). Glucocorticoid treatment is likely to promote hyperglycemia or diabetes mellitus by affecting pancreatic cell functioning and insulin sensitivity (Van

et al., 2009). An in vitro study found that prednisone treated INS-1E cells secreted less insulin in response to a glucose challenge. RU486, a glucocorticoid receptor antagonist, prevented this effect in the presence of prednisone (Linssen *et al.,* 2011). Glucocorticoids can cause insulin resistance via a variety of methods. For instance, by regulating the expression of the PEPCK gene in adipose tissue and the liver and increasing the levels of serum fatty acids. It is commonly known that an increase in fatty acids impairs the body's ability to use glucose and leads to insulin resistance (Franckhauser *et al.,* 1995). Additionally, glucocorticoids reduce insulin sensitivity by impairing glycogen synthase kinase-3, GLUT4 and glycogen synthase translocation, which are all part of the insulin signalling cascade (Van *et al*., 2009).

Targeted Therapy. Targeted therapy aims to modulate signalling pathways or proteins that are abnormal in malignant cells, with the goal of restraining cell proliferation, regulating the cell cycle, or inducing apoptosis (Padma, 2015). However, several targeted drugs are associated with a higher risk of hyperglycemia, and among them, PI3K/mTOR inhibitors are the most notable. The PI3K/Akt/mTOR pathway is frequently activated in various cancer types (Miricescu *et al*., 2020). Inhibiting the PI3K/mTOR pathway also affects insulin signalling, resulting in insulin resistance. One of the mTOR inhibitors used for advanced breast cancer, renal cell cancer and pancreatic neuroendocrine tumours is everolimus, an oral rapamycin analogue. Approximately 10% to 50% of individuals receiving everolimus treatment develop hyperglycemia, with only around 10% of cases experiencing significant hyperglycemia (Morviducci *et al.,* 2018). A meta-analysis of nine randomized clinical trials involving 3879 patients with various cancer types indicated that everolimus was associated with a substantially increased risk of all-grade (RR = 2.60, 95% CI: 2.03 3.31) and high-grade (RR = 3.0, 95% CI: 1.72 5.23) hyperglycemia. The incidences of all-grade and high-grade hyperglycemia related to everolimus were 6.8% (95% CI: 3.4 13.2%) and 2.5% (95% CI: 1.2 4.9%), respectively (Xu *et al.,* 2016). Temsirolimus is another potent and highly specific mTOR inhibitor administered intramuscularly, primarily used in the management of advanced malignancies such as renal cell cancer. The incidence of grade 3 or higher hyperglycemia with temsirolimus is approximately 9% (Bellmunt *et al.,* 2018).

Cancer Immunotherapy. Cancer immunotherapy, which includes a range of treatments like immune checkpoint inhibitors, adoptive cell therapy, oncolytic viruses and cancer vaccines, work by manipulating the immune system to identify and target cancer cells. However, these treatments can potentially result in adverse effects on the endocrine system. For example, some patients treated with antibodies against programmed cell death protein 1 (PD-1) or programmed cell death ligand-1 (PDL-1) have developed insulin-dependent diabetes (Mellati *et al*., 2015). Studies on animals have also demonstrated that the administration of anti-PD-1 or anti-PDL-1 antibodies can induce diabetes in mice (Hofmann *et al.,* 2016). While immune checkpoint inhibitors activate T-cells and bolster the immune response against cancerous cells, they can also lead to autoimmune reactions, including autoimmune endocrine disorders like hyperthyroidism, hypothyroidism and adrenal insufficiency. In rare cases, autoimmune diabetes mellitus has been associated with PD/PD-L1 inhibitors such as nivolumab or pembrolizumab individually or in combination with CTLA-4 and PD-L1 inhibitors like ipilimumab and nivolumab (AlHarbi *et al.,* 2022).

CONCLUSION

In T1DM and T2DM, the risk of various cancers and cancer mortality is elevated. On the other hand, several cancers and cancer treatments are linked to a higher risk of developing diabetes mellitus. This indicates that metabolic and hormonal changes associated with diabetes mellitus are significant contributors to the development of cancer. Several mechanisms have been suggested to elucidate the potential connection between diabetes mellitus and cancer, involving the PI3K/Akt/mTOR and WNT/β-catenin signalling pathways. Furthermore, the interplay between cancer and diabetes mellitus is influenced by factors such as obesity, oxidative stress, inflammation, elevated blood sugar levels, hyperinsulinemia, genetic predisposition and cancer treatments.

FUTURE SCOPE

Understanding the connection between diabetes mellitus and cancer is essential for formulating strategies to reduce the risk of cancer in individuals with diabetes mellitus, or vice versa.

REFERENCES

Abe, R., & Yamagishi, S. I. (2008). AGE-RAGE system and carcinogenesis. *Current pharmaceutical design*, *14*(10), 940-945.

Aggeli, I. K., Theofilatos, D., Beis, I., & Gaitanaki, C. (2011). Insulin-induced oxidative stress up-regulates heme oxygenase-1 via diverse signaling cascades in the C2 skeletal myoblast cell line. *Endocrinology*, *152*(4), 1274-1283.

AlHarbi, A., Alshamrani, M., Khan, M., Alnatsheh, A., & Aseeri, M. (2022). Real-World Experience of Monitoring Practice of Endocrinopathies Associated with the Use of Novel Targeted Therapies among Patients with Solid Tumors. *Medical Sciences*, *10*(4), 65.

Balkwill, F., & Mantovani, A. (2001). Inflammation and cancer: back to Virchow?. *The lancet*, *357*(9255), 539-545.

Bellmunt, J., Szczylik, C., Feingold, J., Strahs, A., & Berkenblit, A. (2018). Temsirolimus safety profile and management of toxic effects in patients with advanced renal cell carcinoma and poor prognostic features. *Annals of Oncology*, *19*(8), 1387-1392.

Bramante, C. T., Lee, C. J., & Gudzune, K. A. (2017). Treatment of obesity in patients with diabetes. *Diabetes Spectrum*, *30*(4), 237-243.

Butler, A. E., Galasso, R., Matveyenko, A., Rizza, R. A., Dry, S., & Butler, P. C. (2010). Pancreatic duct replication is increased with obesity and type 2 diabetes in humans. *Diabetologia*, *53*, 21-26.

Calle, E. E., & Kaaks, R. (2004). Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nature Reviews Cancer*, *4*(8), 579-591.

Calle, E. E., Rodriguez, C., Walker-Thurmond, K., & Thun, M. J. (2003). Overweight, obesity, and mortality from cancer in a prospectively studied cohort of US adults. *New England Journal of Medicine*, *348*(17), 1625-1638.

Chen, W., Wang, S., Tian, T., Bai, J., Hu, Z., Xu, Y., & Shen, H. (2009). Phenotypes and genotypes of insulin-like growth factor 1, IGF-binding protein-3 and cancer risk: evidence from 96 studies. *European journal of human genetics*, *17*(12), 1668-1675.

Currie, C. J., Poole, C. D., & Gale, E. A. M. (2009). The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. *Diabetologia*, *52*, 1766-1777.

Devic, S. (2016). Warburg effect-a consequence or the cause of carcinogenesis?. *Journal of Cancer*, *7*(7), 817.

Franckhauser, S., Antras-Ferry, J., Robin, P., Robin, D., Granner, D. K., & Forest, C. (1995). Expression of the phosphoenolpyruvate carboxykinase gene in 3T3-F442A adipose cells: opposite effects of dexamethasone and isoprenaline on transcription. *Biochemical Journal*, *305*(1), 65-71.

Frasca, F., Pandini, G., Sciacca, L., Pezzino, V., Squatrito, S., Belfiore, A., & Vigneri, R. (2008). The role of insulin receptors and IGF-I receptors in cancer and other diseases. *Archives of physiology and biochemistry*, *114*(1), 23-37.

Gallagher, E. J., & LeRoith, D. (2010). The proliferating role of insulin and insulin-like growth factors in cancer. *Trends in Endocrinology & Metabolism*, *21*(10), 610-618.

Garcia-Jimenez, C., García-Martínez, J. M., Chocarro-Calvo, A., & De la Vieja, A. (2014). A new link between diabetes and cancer: enhanced WNT/β-catenin signaling by high glucose. *Journal of molecular endocrinology*, *52*(1), R51-R66.

Heckman-Stoddard, B. M., DeCensi, A., Sahasrabuddhe, V. V., & Ford, L. G. (2017). Repurposing metformin for the prevention of cancer and cancer recurrence. *Diabetologia*, *60*(9), 1639-1647.

Heidari, N., Miller, A. V., Hicks, M. A., Marking, C. B., & Harada, H. (2012). Glucocorticoid-mediated BIM induction and apoptosis are regulated by Runx2 and c-Jun in leukemia cells. *Cell death & disease*, *3*(7), e349-e349.

Hofmann, L., Forschner, A., Loquai, C., Goldinger, S. M., Zimmer, L., Ugurel, S., ... & Heinzerling, L. M. (2016). Cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy. *European journal of cancer*, *60*, 190-209.

Jamil, M. O. & Mineishi, S. (2015). State-of-the-art acute and chronic GVHD treatment. *International Journal of hematology*, *101*, 452-466.

Kannan, R. (2019). India is home to 77 million diabetics, second highest in the world. *The Hindu*, *14*.

Koppenol, W. H., & Bounds, P. L. (2009). The Warburg effect and metabolic efficiency: re-crunching the numbers. *Science*, *324*(5930), 1029-1033.

Kuniyasu, H., Oue, N., Wakikawa, A., Shigeishi, H., Matsutani, N., Kuraoka, K., & Yasui, W. (2002). Expression of receptors for advanced glycation end- products (RAGE) is closely associated with the invasive and metastatic activity of gastric cancer. The Journal of Pathology: *A Journal of the Pathological Society of Great Britain and Ireland*, *196*(2), 163-170.

Lin, W. W., & Karin, M. (2007). A cytokine-mediated link between innate immunity, inflammation, and cancer. *The Journal of clinical investigation*, *117*(5), 1175-1183.

Linssen, M. M., Van Raalte, D. H., Toonen, E. J., Alkema, W., Van der Zon, G. C., Dokter, W. H., ... & Ouwens, D. M. (2011). Prednisolone-induced beta cell dysfunction is associated with impaired endoplasmic reticulum homeostasis in INS-1E cells. *Cellular signalling*, *23*(11), 1708-1715.

Mellati, M., Eaton, K. D., Brooks-Worrell, B. M., Hagopian, W. A., Martins, R., Palmer, J. P., & Hirsch, I. B. (2015). Anti–PD-1 and anti–PDL-1 monoclonal antibodies causing type 1 diabetes. *Diabetes care*, *38*(9), e137-e138.

Miricescu, D., Totan, A., Stanescu-Spinu, I. I., Badoiu, S. C., Stefani, C., & Greabu, M. (2020). PI3K/AKT/mTOR signaling pathway in breast cancer: from molecular landscape to clinical aspects. *International journal of molecular sciences*, *22*(1), 173.

Morgillo, F., Sasso, F. C., Della Corte, C. M., Festino, L., Manzo, A., Martinelli, E., & Ciardiello, F. (2013). Metformin in lung cancer: Rationale for a combination therapy. *Expert opinion on investigational drugs*, *22*(11), 1401-1409.

Morviducci, L., Rota, F., Rizza, L., Di Giacinto, P., Ramponi, S., Nardone, M. R., & Baldelli, R. (2018). Everolimus is a new anti-cancer molecule: Metabolic side effects as lipid disorders and hyperglycemia. *Diabetes Research and Clinical Practice*, *143*, 428-431.

Padma, V. V. (2015). An overview of targeted cancer therapy. *BioMedicine*, 5, 1-6.

Paulsen, Aass, N., Kaasa, S., & Dale, O. (2013). Do corticosteroids provide analgesic effects in cancer patients? A systematic literature review. *Journal of pain and symptom management*, *46*(1), 96-105.

Pollak, M. (2008). Insulin and insulin-like growth factor signalling in neoplasia. *Nature Reviews Cancer*, *8*(12), 915-928.

Sakatani, T., Kaneda, A., Iacobuzio-Donahue, C. A., Carter, M. G., de Boom Witzel, S., Okano, H., & Feinberg, A. P. (2005). Loss of imprinting of Igf2 alters intestinal maturation and tumorigenesis in mice. *Science*, *307*(5717), 1976-1978.

Sathishkumar, K., Chaturvedi, M., Das, P., Stephen, S., & Mathur, P. (2022). Cancer incidence estimates for 2022 & projection for 2025: result from National Cancer Registry Programme, India. *Indian Journal of Medical Research.*

Soranna, D., Scotti, L., Zambon, A., Bosetti, C., Grassi, G., Catapano, A., & Corrao, G. (2012). Cancer risk associated with use of metformin and sulfonylurea in type 2 diabetes: a meta-analysis. *The oncologist*, *17*(6), 813-822.

Sparvero, L. J., Asafu-Adjei, D., Kang, R., Tang, D., Amin, N., Im, J., & Lotze, M. T. (2009). RAGE (Receptor for Advanced Glycation Endproducts), RAGE ligands, and their role in cancer and inflammation. *Journal of translational medicine*, *7*, 1-21.

Stolzenberg-Solomon, R. Z., Graubard, B. I., Chari, S., Limburg, P., Taylor, P. R., Virtamo, J., & Albanes, D. (2005). Insulin, glucose, insulin resistance, and pancreatic cancer in male smokers. *Jama*, *294*(22), 2872-2878.

Suh, S., & Kim, K. W. (2019). Diabetes and cancer: cancer should be screened in routine diabetes assessment. *Diabetes & metabolism journal*, *43*(6), 733-743.

Takada, M., Hirata, K., Ajiki, T., Suzuki, Y., & Kuroda, Y. (2004). Expression of receptor for advanced glycation end products (RAGE) and MMP-9 in human pancreatic cancer cells. *Hepato-gastroenterology*, *51*(58), 928-930.

Thomas, D. D., Corkey, B. E., Istfan, N. W., & Apovian, C. M. (2019). Hyperinsulinemia: an early indicator of metabolic dysfunction. *Journal of the Endocrine Society*, *3*(9), 1727-1747.

Valko, M., Leibfritz, D., Moncol, J., Cronin, M. T., Mazur, M., & Telser, J. (2007). Free radicals and antioxidants in normal physiological functions and human disease. *The international journal of biochemistry & cell biology*, *39*(1), 44-84.

Van Raalte, D. H., Ouwens, D. M., & Diamant, M. (2009). Novel insights into glucocorticoid-mediated diabetogenic effects: towards expansion of therapeutic options?. *European journal of clinical investigation*, *39*(2), 81-93.

Warburg, O. (1956). On the origin of cancer cells. *Science*, *123*(3191), 309-314.

Xu, J., Ye, Y., Wu, H., Duerksen-Hughes, P., Zhang, H., Li, P., & Xia, D. (2016). Association between markers of glucose metabolism and risk of colorectal cancer. *BMJ open*, *6*(6), e011430.

Xu, J., Ye, Y., Wu, H., Duerksen-Hughes, P., Zhang, H., Li, P., & Xia, D. (2016). Association between markers of glucose metabolism and risk of colorectal cancer. *BMJ open*, *6*(6), e011430.

Yakar, S., LeRoith, D., & Brodt, P. (2005). The role of the growth hormone/insulin-like growth factor axis in tumor growth and progression: Lessons from animal models. *Cytokine & growth factor reviews*, *16*(4-5), 407-420.

Yu, T., Robotham, J. L., & Yoon, Y. (2006). Increased production of reactive oxygen species in hyperglycemic conditions requires dynamic change of mitochondrial morphology. *Proceedings of the National Academy of Sciences*, *103*(8), 2653-2658.

Zhu, B., & Qu, S. (2022). The relationship between diabetes mellitus and cancers and its underlying mechanisms. *Frontiers in Endocrinology*, *13*, 800-815.

How to cite this article: Mayank Patel, Anamika Pandey, Shamshad Ali, Preeti Verma, Prem Kumar and Vikrant Singh Chouhan (2023). The Relationship between Diabetes Mellitus and Cancer. *Biological Forum – An International Journal*, *15*(10): 571-575.