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A Comprehensive Review on Anti-Diabetic Therapy Across Cancer Types from Therapeutic Potential to Risk Factor: Focus on Prostate, Breast Cancer

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ABSTRACT:

There are many biological and epidemiological relations between diabetes mellitus, especially type 2 diabetes (T2DM), and cancer. These include obesity, chronic inflammation, hyperglycaemia and hyperinsulinemia. These interconnected processes affect cancer growth, courses and immunity. Recent research suggests that antidiabetic drugs play a dual role in cancer biology. While some drugs, such as thiazolidinedione and metformin, show medical and protective effects against various types of cancer, others, such as insulin and sulfonylureas, can increase the risk of cancer by activating mitogenic routes. This study emphasizes breast and prostate distortions, with metabolism and cellular routes connecting diabetes and cancer, in brief, therapeutic capacity, clinical benefits and related hazards assess the hazards. Metformin's promising anti -tumour effects, controversial results of sulfonylureas, and increasing clinical importance of insulin, DPP -4 inhibitors and thiazolidinedione have been highlighted. A better knowledge of these interactions can help reproduce the medicine and increase the care of cancer of diabetic patients.

KEY WORRDS: T2 Diabetes Mellitus, Cancer, Hyperglycaemia, Breast Cancer, Metformin, Prostate Cancer, Anti-Diabetic drugs.

INTRODUCTION:

Diabetes and cancer are severe, widespread illnesses that are progressing rapidly around the world. The chronic metabolic disease known as type 2 diabetes is characterized by enduring resistance to the peripheral effects of insulin and decreased insulin secretion cause hyperglycaemia. Nearly, one in nine adults worldwide or 589 million people have diabetes. According, to estimates from the International Diabetes Federation (IDF), the condition is unrecognised to over 252 million persons with diabetes. Over 90% of diabetics have type 2 diabetes mellitus. A collection of diseases where aberrant cells proliferate and spread out of control. Death may ensue if the spread is not prevented.

More precisely, cancer develops when healthy cells get genetic alterations or mutations that interfere with the regular control of the cell cycle, enabling them to:

- Uncontrollably divide
- Invade the surrounding tissues
- Spread (metastasize) through the lymphatic or circulatory systems to other

Organ parts.

It has been estimated that 2,041,910 new instances of cancer would occur worldwide in 2025. Compared to 2020, the incidence of cancer is predicted to rise by 12.8%.

In 2025 According to the NCI, there will be 33 million new instances of cancer annually by 2050, and 5,600 new cases every day. Furthermore, an estimated 107,240 additional cases will occur. Based on a number of studies, T2DM has a higher epidemiological and biological associationwith cancer than T1DM, despite both conditions being linked to an elevated risk of cancer. It is widely recognized that type 2 diabetes and cancer are related. Diabetes increases a person's risk of developing malignancies of the bladder, lungs, prostate, stomach, colon, kidney (renal cell carcinoma), pancreas, ovary, breast, liver (Hepatocellular), and endometrial (uterine).

A possible cause is that risk factors for both cancer and type 2 diabetes are similar, including obesity, smoking, poor diet, hyperinsulinemia, alcohol use, chronic inflammation, aging, and physical inactivity. Chemotherapy, surgery, and radiotherapy are common tools for managing and treating cancer, and they can be used alone or in combination.

In addition to surgery, which is frequently utilized as the first-option intervention for the management of early tumours, radiotherapy is typically employed to treat localized cancers. On the other hand, chemotherapy uses medications that selectively target rapidly proliferating cells with cytotoxic effects.

Although this therapeutic strategy is essential for treating a number of cancer types, it has several drawbacks. Chemotherapeutic medications, for example, might have cytotoxic effects on healthy cells that are proliferating, particularly intestine epithelial and bone marrow cells. One of the other drawbacks of chemotherapy are the emergence of resistance to anticancer drugs. To overcome these constraints, alternative treatments are therefore required. One tactic for overcoming some of the drawbacks of anti-cancer medications are the use of alternative therapeutic agents. such as toxicity and multi drug resistance in malignant cells. However, the exact processes behind the relationship between these malignancies and diabetes remain undefined hyperglycaemia may be one of the risks factor for both conditions. It can cause oxidative stress and the production.

It can cause oxidative stress and the production of advanced glycated end products (AGEs); hyperinsulinemia, which typically happens as a result of resistant insulin production (impaired insulin function) or exogenous insulin; inflammation; and obesity. Anti-Diabetic medications and lifestyle changes are typically the basic components of treatment for type 2 diabetes. BY encouraging the secretion of insulin by pancreatic βcells, raising insulin sensitivity to peripheral tissues, encouraging the uptake of glucose into cells, and decreasing the reabsorption of glucose from renal tissues and the intestine, these medications reduce elevated blood glucose levels and other related problems. It's interesting that these medications have been shown to have anticancer properties because they may prevent the disease's progression. This study reveals some of the metabolic links between cancer and diabetes, as well as the detrimental (repurposing) and potential risks in the use of antidiabetic drugs for cancer cell management and therapies. Some research has indicated that antidiabetic drugs can act as a risk factor in either the onset or progression of cancer, but their action against cancer cells surpasses their risk the impacts in the growth of this disease.

Numerous kinds of anti-diabetic medications, alpha-glucosidase inhibitors, TZDs2 Inhibitors, DPP-4 Inhibitors, GLP-1Ras, sulfonylureas (Sus), Biguanides, and thiazolidinediones, have been shown to have beneficial effects in the treatment of various types of cancer. As, well as the risk factors have been occurred. Therefore, the aim in this review is based on the various types of cancers and their therapies, risk factors by the anti-diabetic medications. Particularly, one anti-diabetic medication for management and most risk factors caused by one anti-diabetic medication for various types of cancer.

COMMON METABOLIC AND CELLULAR PATHWAYS LINK BETWEEN DIABETES AND CANCER:

There are numerous metabolic and signaling pathways that alter basic cellular processes.and are similar to cancer and diabetes. It provides up the possibilities for the use of antidiabetic medications in the treatment of cancer.It has been determined that the correlation between diabetes and cancer depends on a number of the disease's hormonal (insulin, IGF1, adipokines), immunological (inflammation), or metabolic (hyperglycemia) features, as well as particular therapies.Mammalian target of rapamycin (mTOR) signalling, transforming growth factor (TGF)β signaling, interleukin (IL)6 signaling, hypoxia inducible factor (HIF) signaling, platelet-derived growth factor (PDGF) signaling and Wnt (winglesstype MMTV integration site family) Signalling are the main pathways.

CELLULAR PATHWAYS:

1. PI3K/Akt/mTOR SIGNALING PATHWAY:

The mTOR signaling system controls several physiological processes, including metabolism, cell division, and growth, by integrating external and intracellular signals. While, regulating anabolic processes like the production of lipids, proteins, and organelles, mTORC1 suppresses catabolic processes like autophagy. Through, the PI3K/AKT signaling pathway, growth factors including insulin and insulin-like growth factor (IGF) can convey signals that activate mTORC1.mTORC1 is triggered when AKT suppresses the Tuberous Sclerosis Complex (TSC) 1/2, which increases cell growth and division.

ROLE IN CANCER:

• Many malignancies are characterized by abnormal activation of mTOR signaling, which is caused by component mutations of the mTOR pathway, especially in initial regulators and downstream effectors.

• mTORC1 angiogenesis activation, which causes tumour growth in both in vivo and invitro cell lines.

• Oncogene activation mutations (Ras, Raf, PI3K, AKT) and mutations that abolish function in genes that regulate tumour suppression (TSC1/2, PTEN) lead to dysregulation of the mTOR pathway.

ROLE IN DIABETES:

• The mass and activity of pancreatic β cells, which are essential for maintaining glucose homeostasis, are influenced by mTORC1 signalling.

• Insulin resistance, a major characteristic of type 2 diabetes, is linked to dysregulated mTORC2 signalling.

• Elevated mass and insulin production are the initial benefits of enhanced mTORC1 activity for β-cell function; however, sustained activation can cause β-cell malfunction and accelerate the development of diabetes.

2. WNT (wingless type MMTV integration site family)

• Although it controls cellular division and physiological events such embryonic development, cell migration/polarization, maintenance, growth, and the epithelial mesenchymal transition of stem cells, the Wnt/β-catenin signaling system is a key mechanism.

• Any change or alterations in specific parts of this pathway is linked to birth defects in humans, the development of various cancers (by altering the behavior of cancer stemcells), including leukemia, colon cancer, hepatocarcinomsssa, and other metabolic diseases like type 2 diabetes.

ROLE IN DIABETES:

• By enhancing nucleus accumulation of βcatenin, hyperglycemiaa feature of diseases like obesity and diabetesimproves Wnt signaling and promotes the ongoing expression of gene essential for cell survival and proliferation.

• Wnt/β-catenin signaling is enhanced by hyperglycemia, which leads to βcatenin acetylation, nuclear retention, and growth and survival gene activation.

• Constitutive activation in malignancies is driven by mutations in APC/Axin/β-catenin. By demonstrating that hyperglycemia can directly alter malignancy associated

Signal pathways, this method contributes to the explanation of the epidemiological association between diabetes and a higher risk of cancer.

ROLE IN CANCER:

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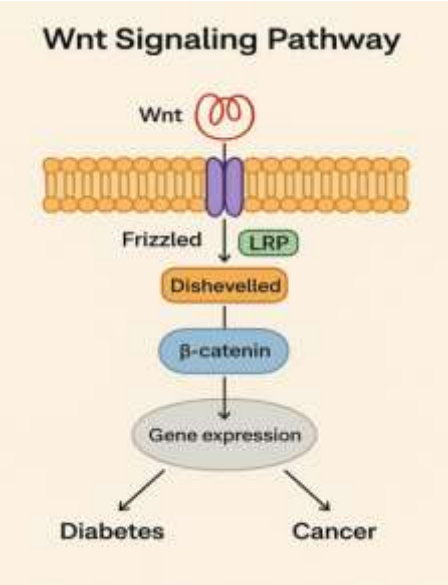

FIGURE NO.01: WNT SIGNALING PATHWAY

3. IGF-1 SIGNALING PATHWAY:

A key factor in both diabetes and cancer is the IGF-1 signalling pathway. The IGF-1 signalling pathway is a critical regulator of cell growth, metabolism, and survival. It is initiated when IGF-1 binds to the IGF-1 receptor (IGF-1R) on the cell surface, leading to receptor autophosphorylation and activation of downstream signalling cascades, including:

• PI3K/Akt/mTOR Pathway: Promotes cell survival, protein synthesis, and metabolism.

• MAPK Pathway: Stimulates cell proliferation and differentiation.

These pathways are essential for normal cellular function and development.

ROLE IN DIABETES:

• Type 2 diabetes is characterized by insulin resistance, which modifies the ratio of insulin to IGF-1 signalling.

• IGF-1R and its downstream pathways may be persistently activated by chronic hyperinsulinemia, which can encourage aberrant cell development and proliferation.

• Furthermore, glucose metabolism is impacted by compromised insulin/IGF-1indicating which leads to systemic metabolic impairment and elevated oxidative stress, both of which hasten cell death and inflammation (inflammaging).

ROLE IN CANCER:

• Many types of cancer have an overactive IGF-1 signalling pathway.

• Increased production of IGF-1 or IGF 1R inhibits apoptosis (programmed cell death), increase tumour cell survival, and promotes uncontrollable cell proliferation.

• In malignant cells, activation of the PI3K/Akt/mTOR and MAPK pathways promotesdevelopment of tumors and increases resistance to radiation and chemotherapy. Moreover, disruption of the insulin/IGF axis is frequently linked to malignancies linked to metabolic conditions such obesity and type 2 diabetes.

• The GH/insulin/IGF1 signaling pathway's dual function of promoting growth and controlling metabolism emphasizes its contradictory role in both normal development and the advancement of disease. Tightly controlled signalling is necessary for healthy physiology, but long-term activation leads to the illnesses like cancer and diabetes. Therefore, altering this route is a potentially effective treatment strategy for cancer and age-related metabolic diseases.

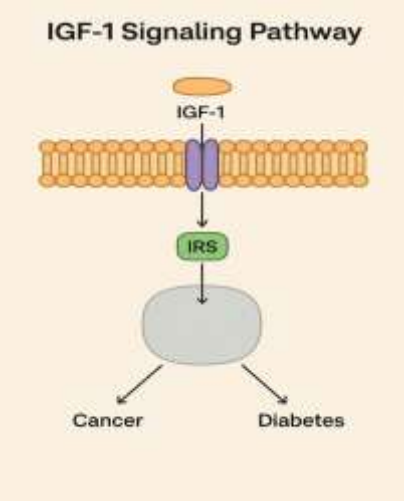

FIGURE NO.02: IGF-1 SIGNALING PATHWAY

METABOLIC/PATHOPHYSIOLOGICAL CONDITIONS LINK BETWEEN CANCER AND DIABETES:

1.HYPERGLYCAEMIA:

• Since it weakens tumor suppressor genes and causes oxidative stress and DNA damage, elevated levels of glucose (hyperglycaemia) may encourage cancer.

• It results in the production of AGEs, which attach to RAGE proteins to cause angiogenesis, inflammatory processes, and tumour growth.

• Additionally, hyperglycemia causes TXNIP, which lowers antioxidant defenses, inhibits the immune system, and supplies energy to support the proliferation of cancer cells.

2.HYPERINSULINEMIA:

• Insulin and IGF1 activate the PI3K/Akt/mTOR and RAS/RAF/MEK/ERK pathways by binding to their respective receptors (IR, IGF-IR, and hybrid versions).

• These mechanisms prevent apoptosis and increase cell viability and division, which are important factors in tumour formation.

• In those with type 2 diabetes, elevated insulin levels are associated with a higher risk of developing pancreatic, colon, breast, and liver malignancies.

• Increased ROS, weakened adhesion between cells (due to decreased Ecadherin), enhanced invasion, and epithelial mesenchymal transition (EMT) are all caused by elevated blood glucose levels.

3.INFLAMMATION AND OXIDATIVE STRESS:

• Chronic inflammation and oxidative stress are caused by persistent hyperglycaemia through the excessive activation of pathways such as polyol, AGE-RAGE, protein kinase C, and HBP.

• ROS induced DNA damage, instability of the genome, and tumorigenesis are further enhanced by inflammatory cytokines such as TNF-α and IL-6 encouraging signals, for instance through NF-kB.

TABLE: NO.01 DIABETES-RELATED MECHANISMS INVOLVED IN CANCER PROGRESSION

TRIGGERS	MEDIATORS	EFFECTORS
Chronic inflammation	Inflammatory cytokines, such as TNF-α and IL-6 Insulin signalling	Increased cell proliferation, angiogenesis, and invasion
Insulin resistance	Insulin signalling pathways	Increased cell proliferation and survival
Hyperglycaemia	Advanced glycation end products (AGEs)	DNA damage, oxidative stress, and inflammation.
Obesity	Adipokines, such as leptin and adiponectin	Increased cell proliferation, inflammation, and angiogenesis

ANTI-DIABETIC MEDICATIONS AND CANCER:

Many studies have examined the complicated interaction between antidiabetic drugs and their possible effect on cancer risk.

The cancer risks listed include the following summarizes the ways in which various antidiabetic medication classes, including thiazolidinediones (TZDs), sulfonylureas (SUs), and biguanides (metformin), are linked to the risk of cancer.

METFORMIN: Metformin is a biguanide analogue that mainly lowers the levels of glucose in people with type 2 diabetes. It works by increasing the absorption of glucose by the body, decreasing hepatic gluconeogenesis, and improving the sensitivity of insulin.

Its possible anticancer properties are well known.

According to numerous research, metformin may lower the chance that cancer may start and spread. It uses a number of methods to achieve its goals, including:

(i) AMPK Activation: Metformin triggers the activation of AMP-activated protein kinase (AMPK), which controls the metabolism of cellular energy and suppresses the proliferation of cancer cells. (ii) Insulin Sensitivities: Metformin indirectly counteracts the growth-promoting effects of insulin and insulin-like growth factor 1 (IGF-1) by increasing insulin sensitivity and lowering hyperinsulinemia.

(iii) Anti-inflammatory effects: Metformin's anti-inflammatory effects may be a contributing factor to its anti-cancer effects.

Metformin shows notable effectiveness in lowering incidence and raising survival rates in a number of malignancies, such as those of the pancreas, colon, stomach, liver, breast, endometrial, lung, and prostatefocusing on several physiological pathways, involving as AMP-activated protein kinase (AMPK), AKT/mTOR signalling, and fatty acid production, is thought to be the cause of its anti-cancer properties.

1.METFORMIN:

Metformin blocks the AKT/AKT pathway and stimulates AMPK, a crucial regulator of energy production in cells metabolism. mTOR pathway, which inhibits the growth and multiplication of cancer cells. Furthermore, through pathways involving the activation of cMYC, Hypoxia-Inducible Factor (HIF)-1, and DICER1, metformin-induced AMPK activation reduces the proliferation of cancer cells [89]. Notably, metformin suppresses mTOR activation via Rag GTPases independently of AMPK and TSC1/2.Despite its ability to manage blood sugar, the popular antidiabetic medication metformin has demonstrated strong anti-cancer properties.

Metformin improves sensitivity to treatments and reduces androgen-driven development in prostate cancer. It inhibits the metabolism of tumor cells in breast cancer, especially those that are triple-negative and hormone receptor-positive. All things considered, metformin shows encouraging treatment and prophylactic effects against these malignancies.

2.SULFONYLUREAS:

Insulin release from pancreatic β-cells is stimulated by sulfonylureas, a family of oral hypoglycaemic medications used to treat type 2 diabetes.

Lately, the possibility of repurposing Using sulfonylureas in the treatment of cancer has drawn interest. Nonetheless, there is a complicated relationship between sulfonylureas and the risk of cancer.

According to certain studies, sulfonylurea using T2DM patients had an increased risk of developing cancer, which may be related to their usage of metformin as a comparator. However, Haggstrom et al. (2017) found that male T2DM patients taking sulfonylureas had a lower chance of developing cancer than those not taking antidiabetic medications.

Long-term use of sulfonylureas may raise the risk of pancreatic cancer, according to some data. This could be because persistent hyperinsulinemia encourages the formation of tumours. There are conflicting results on prostate and breast cancer; some studies indicate a neutral effect, while others suggest a little higher cancer risk, which is probably caused by insulin-mediated pathways.

Sulfonylureas are mainly assessed for their indirect impact on cancer through metabolic modification rather than their efficacy as chemotherapy agents.

3.THIAZOLIDINEDIONES:

Using PPAR-γ-dependent and independent pathways, thiazolidinediones (TZDs), including troglitazone, rosiglitazone, and pioglitazone, demonstrate anticancer activity including breast, thyroid, lung, and prostate cancers. They alter important signalling pathways like PTEN/AMPK and AKT/mTO,

suppress cell division, and trigger apoptosis. Studies have shown inconsistent results despite their efficacy, with PPARγ occasionally having tumour-promoting roles. Furthermore, TZDs inhibit genes such as VEGF, PGE2 receptor, and insulin receptor. Particularly, aromatase activity is decreased by ciglitazone in androgen-dependent prostate cancer.

Furthermore, in clinical trials, TZD compounds such as netoglitazone and efatutazone have shown increased anticancer activity. Ciglitazone has been shown to decrease aromatase activity in prostate cancer, while TZDs may prevent tumor growth in breast cancer by encouraging cell differentiation and inhibiting angiogenesis. Despite showing promise, inconsistent results and possible side effects continue to restrict TZDs' clinical efficacy.

4. INSULIN AND ANALOGS:

Although treatment with insulin is crucial for managing diabetes, there are worries

that it may increase the risk of cancer, particularly when used excessively and over an extended period of time. Because, of their mitogenic actions and biological similarity to IGF1, hyperinsulinemia and some insulin analogs (such as glargine) may encourage the formation of tumours.

Insulin activates IR and IGF-1R, which promote cell division and prevent apoptosis. Additionally, it increases free IGF1 and decreases IGFBPs, which may promote tumorigenesis even more.

5. DPP-4 INHIBITORS:

The use of DPP4 inhibitors to treat type 2 diabetes has produced conflicting results on their relationship to cancer risk. Some research points to a possible connection to pancreatic cancer as well as a dose dependent effect on colorectal cancer, where large dosages increase risk and low levels decrease it. Furthermore, DPP-4 inhibitors have no effect on non-melanoma skin cancer but may reduce the incidence of melanoma by 23% when compared to sulfonylureas. However, results are still mixed, and further study is required.

BREAST CANCER:

ASSOCIATION BETWEEN BREAST CANCER AND DIABETES:

Breast cancer is the most common cancer among women in industrialized nations, and as the Western way of life becomes more popular, its prevalence is also rising quickly in emerging nations. As a metabolic disease, diabetes has a strong correlation with a higher risk of breast cancer. Diabetes is linked to increased rates of both development and death of breast cancer, according to a substantial body of epidemiological research.

Diabetes may promote the growth of tumours.

It was challenging to administer radiation therapy to women with diabetes. Diabetes consequently contributes to a later diagnosis and fewer options for treatment, which results in a more severe form of breast tumor and a higher death rate.

” METFORMIN AS THE MOST CLINICALLY UTILIZED WITH POTENTIAL THERAPIES”

Metformin, a medication belonging to the biguanide family that lowers blood sugar and enhances peripheral tissues' sensitivity to insulin, may also have anti-cancer properties.

MECHANISM FOR THE ANTI-CANCER EFFECTS:

Metformin's anticarcinogenic properties have been linked to a number of processes, including the induction of apoptosis or cell cycle arrest of stem cells, the lack of protein synthesis, the activation of the adenosine monophosphate activated protein kinase AMPK/LKB1 pathway, the inhibition of the unfolded protein response (UPR), or the quick initiation of the defense mechanism. The human tumor suppressor liver kinase B1 (LKB1), also known as serine/threonine kinase 11, directly phosphorylates and activates AMPK, which is a crucial metabolic sensor. In specific tissues such muscle, liver, and adipose tissue, AMPK controls the metabolism of fat and glucose.

CLINICAL STUDIES AND ANALYSIS:

Epidermiological research on metformin users revealed that they had increased cancer rates of survival and decreased cancer incidence. Additionally, preclinical testing has demonstrated metformin's anti-tumorigenic action on breast cancer. The-five year disease-free survival rate (DFS) was 85.8%, 96.1%, and 73.0%, and the five- year overall survival (OS) was 87.3%, 97.1%, and 73.3%, respectively, for the non-diabetes group, metformin group, and insulin group, according to a recent retrospective cohort study of 3553 patients with breast cancer and diabetes mellitus (Cancers 2024, 16, 299 8 of 17). This offers a theoretical foundation for the introduction of metformin for treating cancer and increase the chance of survival. In a meta-analysis by Yang et al., assessing the prognostic value of metformin various cancers, including31,031breast cancer patients (3936 metformin users), metformin therapy demonstrated potential survival benefits compared to non-metformin users, including overall survival (HR = 0.77, 95% CI: 0.69–0.86) and progression-free survival (HR = 0.64, 95% CI: 0.44–0.91).

INSULIN & SULFONYLUREAS THERAPY AS A RISK FACTOR IN BREAST CANCER:

The impact of elevated insulin and insulin-like growth factors (IGF) on increasing carcinogenesis has been highlighted by experimental models.

MECHANISM FOR THE ANTI-CANCER EFFECTS:

Peptides called the hormone insulin and IGF are essential for glucose homeostasis, cell division, metabolism, and proliferation apoptosis as well.IGF-1, IGF- 2, and insulin are the three main ligands involved in the insulin/IGF signaling system.

These ligands can interact with at least six receptors, including the type 1 IGF receptor (IGF-1R), insulin receptor A (IR-A), insulin receptor B (IR-B), IGF with IR-A hybrid receptors, IGF with IR-B hybrid receptors, and IR-A with IR-B hybrid receptors

In along with activating physiological and mitogenic signaling pathways, insulin also inhibits sex hormone-binding globulin and insulin-like growth factor-binding protein (IGF-BP) (SHBG). Breast tumours that depend on steroid hormones and IGF are exacerbated by this downregulation. By activating mitogenic signaling pathways, elevated blood levels of insulin also promote angiogenesis and proliferation of tumours.

CLINICAL STUDIES AND ANALYSIS:

Mu et al. examined the impact of insulin therapy in a retrospective research involving 462 people with diabetes mellitus and 1644 patients without the disease. Even after taking into account all of the previously listed factors, the five-year risks for mortality (HR = 1.68, 95% CI: 1.03–2.75; p = 0.038) and recurrence (HR = 1.61; 95% CI: 1.07–2.41; p = 0.021) in this study showed a significant rise in the insulin subgroup when compared to the non-insulin subgroup. Insulin users had a statistically significant higher risk of breast cancer recurrence than non-users, according to a meta-analysis of these studies (HR = 1.43, 95% CI: 1.13–1.80; p = 0.003) [32]. However, another study found the opposite outcome.

SULFONYLUREAS ANALYSIS AND STUDIES:

Since the 1950s, sulfonylureas (SUs) have been used to treat diabetes mellitus.16,397 women with early-stage or stage II breast cancer, ages 66 to 80, had been enrolled in the study by the authors. The hazard ratios were estimated using time-dependent Cox proportionality hazard models. Sulfonylurea use was linked to increased chances of dying from breast cancer (HR = 1.49, 95% CI: 1.00–2.23). Nonetheless, there was no difference in the risk of breast cancer death or recurrence between sulfonylurea users and non- users among the diabetic women undergoing treatment.

ASSOCIATION BETWEEN PROSTATE CANCER AND DIABETES:

According to the American Cancer Society's most recent study, prostate cancer is the second most common cause of cancer-related deaths among American men and the cause of the greatest number of cases newly diagnosed in the country. There is compelling evidence to support the link between hyperglycemia and a lower risk of prostate cancer, according to a metaanalysis that included 45 research (29 cohort and 16 case-control studies) with 8.1 million individuals and 132331 cases of prostate cancer. Additionally, a meta-analysis has demonstrated that the negativecorrelation between diabetes and prostate tumors is restricted to incidence rather than death rates, and that individuals who have diabetes who also have prostate cancer have a poorer prognosis.

METFORMIN & THIAZOLIDINEDIONES ARE THE MOST CLINICALLY UTILIZED WITH POTENTIAL THERAPIES:

The first-choice medication for type 2 diabetes mellitus is metformin (Met).

MECHANISM FOR ANTI-CANCER EFFECTS:

Metformin prevented tumor cells from proliferating in the animal models, but not PC cells from migrating. Another way to stop growth is to stop the G0/G1 cell cycle.

Metformin lowers pRb and cyclin D1 levels. phosphorylated and raises the expressionof the p27kip protein. Metformin also works well to reduce insulin and IGF-1 levels.

By activating the FOXO1 subunit of the androgen receptor, these hormones can hormones can promote the growth of prostate cancer. Metformin suppresses PI3K/AKT/mTOR and induces an arrest in the cell cycle by upregulating REDD1, which is controlled in development and DNA response-1. These activities promote apoptosis and inhibit tumours. Met also delays cell aging by inhibiting NF-B.

CLINICAL STUDIES & ANALYSIS:

Pre-clinical study results are briefly discussed, along with how they relate to currently accessible clinical trials. The majority of anti- diabetic medications do not raise hazards when treating PC patients, according to available research and meta-analyses. Overall survival among PC patients treated with metformin improved, according to the findings of all meta-analyses conducted over the previous five years, which were published by He et al. in 2019, Coyle et al. in 2016, Xiao et al. in 2017, and Stop sack et al. in 2016. Additionally, the recent three big meta-analyses are expected to reduce the recurrence of PC among metformin users. METAL (metformin and lifespan), a randomized, double-blind, placebo -controlled study, is another intriguingly structured trial that aims to pinpoint the molecular processes behind the impact of metformin on PC. Before undergoing a prostatectomy, the authors want to evaluate 100 PC patients in two groups: those taking metformin and those receiving a placebo. Prostate cancer was not the focus of earlier research in this field, or it was retrospective. As a result, only recent, prospective research may offer definitive findings about the impact of metformin on PC development.

THIAZOLINEDINEDIONES:

Through the inhibition of cyclin D1 expression and the activation of the p38 MAPK and NFB pathways, pioglitazone was able to inhibit PC cell lines in in vitro experiments. There is inconsistent clinical data about the incidence of prostate cancer among pioglitazone users. There was no correlation found between the incidence of prostate cancer and previous pioglitazone use in a Taiwanese populationbased study of 3513 PC patients over 40, 178 of whom received PGZ treatment, and one control subject per case.

INSULIN THERAPY AS A RISK FACTOR IN PROSTATE CANCER:

Insulin resistance is common in type 2 diabetic patients, and the stage of the disease also affects blood insulin levels.

MECHANISM FOR THE ANTI-CANCER EFFECTS:

Insulin plays a crucial role in type 2 diabetes, even though metformin is the suggested primary treatment. This process starts when the protein tyrosine kinase domain is activated, causing the insulin receptor substrates 1 and 2 (IRS1 and IRS2) to become autophosphorylated. This routes the signal to the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) Akt signalling pathways. The PI3Ksignalling cascade synchronizes cellular processes such protein synthesis, glucose uptake and use, and proliferation of cells with systemic nutritional status.

CLINICAL STUDIES AND ANALYSIS:

In an observational study of 310 patients, 54 of whom died from prostate cancer during a 5-year follow-up, it was found that hyperinsulinemia and type 2 diabetes had a statistically significant link with deadly prostate cancer.

As of right now, the most intricate meta-analysis of 205,523 male patients and 7053 PC instances shows a correlation between insulin use and PC risk when compared to other anti-diabetic medications (RR=0.89,95%CI:0.72–1.09).There is no proof that those who use large amounts of insulin have a higher PC risk than people who don't (RR1.26, 95%CI:0.86–1.84).[54]

CONCLUSION:

The importance of addressing general risk factors and treatment overlap is exposed by complex links between diabetes and cancer. Through processes including AMPK activation, MTOR prohibition, and tumour-promoting metabolic routes, suppression of antidiabetic drugs, especially metformin-especially strong anticancer capacity. Treatment, on the other hand, treatments such as insulin and sulfonylureas raise concerns about cancer incidence and progress, especially in hormone-sensitive tumours such as prostate and breast cancer. The results of thiazolidinediones and more recent drugs are still encouraging, which reflects the need for more research. Evidence as a whole indicates that although antidiabetic therapy can also serve as a risk factor with a treatment option, it can also provide metabolic control and prevention of cancer if it is carefully chosen based on the patient's characteristics and types of cancer. Confirm these results and require safe, concentrated treatment plans, more possible and molecular research.

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