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Effect of DNA Damage on the Development of Diabetes Mellitus due to Ionizing Radiation Exposure

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Abstract

Exposure to ionizing radiation destroys several biological processes by disturbing the membranes of cells and causing damage to DNA, proteins, and mitochondria. Increasing the use of ionizing radiation-based treatment and diagnosis techniques has been associated with the increased chronic diseases among healthcare occupational and patients. However, numerous factors such as duration of exposure, radiation dose, dose rate, the target body organs, and the person's age impact the ionizing radiation-induced chronic effect. Exposure to ionizing radiation has various harmful effects on healthy tissues; long-term exposure to radiation increases the risk of carcinogenesis and autoimmune diseases such as diabetes. A recent study has also highlighted its potential role in the development of diabetes. This review examines the linkage between radiation-induced DNA damage and diabetes and Explores how radiation can contribute to the emergence and worsening of this chronic metabolic disorder. This review study aims to offer an exhaustive summary of how radiation-induced DNA damage promotes diabetes hazards, highlighting areas for future studies. Also, taking oral antioxidants to protect from radiation-induced DNA damage and mitigate oxidative damage and inflammatory markers after radiation exposure may reduce the incidence of diabetes.

Radiation can cause damage to DNA through ionization, which creates free radicals that attack the DNA structure, leading to genetic mutations or breaks in the DNA strands. This damage is most dangerous when it occurs in cells responsible for glucose regulation or insulin production, contributing to the development of diabetes.

Keywords: Ionizing radiation, DNA damage, Diabetes, Free radicals, Mutations.

Introduction

Millions of individuals are exposed to radiation from artificial sources resulting from diagnostic radiation, radiotherapy, and nuclear medicine. In addition, the emission of radiation from burning coal in a nuclear reactor, nuclear power generation stations, and for war purposes [1]. Also, individuals are exposed to radiation from terrestrial sources, such as radioactive elements found in rocks and soil; these radioactive materials exist in air, water, and animals and exist in the human body due to inhalation or ingestion [2]. Exposure to ionizing radiation disrupts the redox balance of cells, leading to damage in membranes, proteins, and mitochondria, thereby disrupting several biological processes [3]. Ionizing radiation has the capacity to directly interact with specific target molecules such as DNA, lipids, and proteins or induce changes in oxidative events and cellular biological activities through its interaction with water molecules. The liver is notably sensitive to radiation, ranking as the second most radiation-sensitive organ after the lymph, bone marrow, gastrointestinal tissue, embryos, gonads, and kidneys. As a vital mammal organ, the liver fulfils essential functions, including protein synthesis, bile production, glycogen storage, waste elimination, and nutrient metabolism [4]. Radiation has the potential to directly influence the DNA in the liver, resulting in damage to the DNA structure and impacting biological functions. Additionally, it can directly affect the side chains in the protein structure, causing changes in the spatial structure of the peptide chain. Furthermore, radiation can disrupt chemical bonds in steroid molecules, phospholipids, and lipids, and interference with metabolism can lead to cell death. Ionizing radiation can cause acute disease by reducing red blood cell production and damaging the digestive system, as well as damaging proteins by forming hydroxyl free radicals from water in aqueous-air solutions. These radicals then form protein radicals, leading to damage. In biological systems, this damage is especially

significant because proteins are the main targets of these radicals. The reaction between hydroxyl radicals and proteins happens quickly and usually results in losing the protein's biological function [5].

Ionizing radiation, whether from terrestrial or artificial sources, can cause a range of genetic modifications through different mechanisms, including single-strand breaks, double-strand breaks, and oxidative stress [6, 7]. These disorders in DNA integrity have been shown to impact cellular function and promote the development of numerous health conditions [8, 9, and 10].

Diabetes mellitus is a prevalent metabolic disorder that occurs due to a deficiency in the secretion of insulin by the beta cells of the pancreas or as a result of a poor response to it by the body's cells, thus raising blood glucose levels. It is called the silent disease because the symptoms of the disease are delayed for several years, so researchers have attempted to construct an accurate diabetes prediction model over time [11]. Type 1 diabetes (previously known as juvenile diabetes) occurs when the body cannot produce insulin (as a result of the destruction of beta cells in the pancreas by the body's immune system), also known as insulin-dependent diabetes mellitus, requiring the individual to use an insulin pump or inject insulin. On the other hand, type 2 diabetes, or non-insulin-dependent diabetes mellitus, arises from insulin resistance, where cells do not respond properly to insulin, whether or not there is an absolute insulin deficiency. In 2017, Type 2 diabetes affected 6.3% of the global population and ranked as the ninth leading cause of death [8]. The economic impact of this disease is projected to increase from 1.8% of global GDP in 2015 to 2.2% by 2030 [12].

Diabetes mellitus (DM) could be affected by various environmental conditions, lifestyle, and genetic factors [13]. Recent research has begun to explain how radiation-induced DNA damage might interact with these factors to exacerbate the pathogenesis of diabetes; this intersection is crucial for cancer survivors who have had radiation therapy since they have an increased risk of type 2 diabetes [14]. Radiotherapy (RT) is a well-established and frequently used treatment for patients diagnosed with early-stage extranodal marginal zone lymphoma of the mucosa-associated lymphoid tissue (EMZL) and follicular lymphoma (FL) in the stomach or duodenum [15, 16]. The main role of the pancreas is to regulate blood glucose levels, with

insulin produced by the beta cells helping to lower these levels. Therefore, damage to the pancreas can lead to diabetes [17]. Because the pancreas is situated close to the stomach and duodenum, it may be inadvertently exposed to radiation when the gastroduodenal area is treated [15, 16].

A recent 2022 study by [18] found that patients who underwent radiotherapy for gastroduodenal indolent lymphoma had a higher risk of developing diabetes compared to those who did not. Other studies have indicated that diabetes significantly increases the risk of radiation damage following radiotherapy for various tumors. This is due to urogenital, gastrointestinal, and breast cancer treatments being more prevalent among patients with diabetes. [19, 20 and 21].

In this review, we will examine the linkage between radiation-induced DNA damage and diabetes, Explore how radiation can contribute to the emergence and worsening of this chronic metabolic disorder, and examine the genetic changes that have been found in human cells.

Biological Effect of Ionizing Radiation

Deterministic Effects and Stochastic Effects

The deterministic effects, also known as the acute and sub-acute effects, are characterized via non-linear dose responses figure [1]. These effects do not happen below a specific threshold radiation dose [22, 23]. Deterministic effects are most important in radiotherapy; healthy tissue therapy doses are finite to avoid these effects [24]. Deterministic effects result from significant cell damage or death.

The physical effects will see when the extent of cell death is adequate to impair organ or tissue function [25]. Radiobiological and clinical research has demonstrated that deterministic effects, such as cataracts, acute effects, and malformations, only occur at doses exceeding a certain threshold. Studies reported that in the Biological Effects of Ionizing Radiation, the dose and reference values are set between 0-100 mGy to prevent these effects and are considered low-dose ionizing radiation [26, 27]. Studies reported that in the Biological Effects of Ionizing Radiation, the dose and reference values are set between 0-100 mGy to prevent these effects and are considered low-dose ionizing radiation. Other studies showed that the

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ionizing radiation dose values between 100-1 mGy are considered moderate dose radiation, and ionizing radiation dose values above 100 1Gy are considered high-dose ionizing radiation [28, 29 and 30]. Till the recent past, it was anticipated that low doses of ionizing radiation also induce long-term health risks, while stochastic effects, also known as chronic effects see (figure 1). The stochastic effect is damage that happens to genetic material even in low ionizing radiation doses, and these effects are probabilistic and do not have any threshold dose [31, 32 and 33]. The occurrence of the stochastic effects rises with the dose received; these effects occur due to small exposure received over a long time that causes genetic effects via altering information of the genetic code, which causes various cancers and deformation [34, 35 and 36].

Figure 1: showing deterministic and stochastic effects of ionizing radiation.

Mechanisms of Radiation-Induced DNA Damage

It is important to consider several individual genetic factors that may increase susceptibility to radiation-induced reactive oxygen species (ROS) formation and DNA damage beyond the accepted radiation risk level. Factors affecting individual radiation sensitivity include genotype, diabetes, age, and others [37, 38].

Human cells can change when they are exposed to radiation in the environment. These changes can affect how genes are regulated and put the human epigenome at risk [38].

DNA Mutations are crucial to both natural evolution and genetic disorders. Despite the protection of a cellular environment, exposure to various external agents such as sources of radiation, electric fields, mutagenic compounds, free radicals, or metallic centers causes DNA mutations [39].

Certain gene mutations can make individuals more susceptible to diseases like diabetes, especially in the presence of environmental factors like ionizing radiation. For example, mutations in genes responsible for insulin secretion (e.g., INS, KCNJ11) or insulin resistance (e.g., PPARG, LEPR) can contribute to Type 2 diabetes (T2D).

Additionally, mutations in genes related to oxidative stress response mechanisms (like SOD2, GPX1) may exacerbate the effects of radiation-induced damage, leading to increased risk of metabolic diseases, including diabetes.

Radiation can cause chromosomal breaks, translocations, and inversions, which may affect genes involved in metabolic regulation, potentially contributing to the development of diabetes. For example, translocations involving the INS gene may interfere with insulin production, a hallmark of both Type 1 and Type 2 diabetes. Most research has concentrated on DNA damage caused by ionizing radiation (IR) at the linear DNA level, particularly regarding cancer development, mutations, and the subsequent effects on cell death and tissue damage. However, the human genome is not just a linear sequence; it also has a three-dimensional (3D) structure that affects transcription, replication, and repair processes [40]. DNA damage can result in deletions, translocations, and other genomic abnormalities, which may disrupt regulation or directly mutate genes, potentially leading to diabetes or cancer [41].

Clustered DNA damage is more cytotoxic and mutagenic than isolated damage, but studying it has been challenging due to the complex variety of induced lesions and their random distribution across the genome. However, it is generally accepted that radiation-induced clustered DNA damage, which includes both non-double-strand break (non-DSB) and double-strand break (DSB) lesions, is often poorly repaired or not repaired at all. This contributes to the more significant mutagenic and cytotoxic effects of clustered lesions compared to isolated ones. Improper rejoining of double-strand breaks (DSBs) can result in chromosome translocations, some of which may lead to cancer. Thus, effective DNA repair is crucial for maintaining genome integrity by preventing chromosome translocations and alterations to genetic material. High linear energy transfer (LET) charged particle radiation is more cytotoxic per unit dose than low LET radiation because it induces more clustered DNA damage [42].

Direct and Indirect Damage of Ionizing Radiation

Ionizing radiation causes damage to DNA, which is considered a significant target of biological effects ionizing radiation, by both direct and indirect damage [43]. In direct damage, charged particles such as protons, electrons, alpha-particles, and beta-particles deposit their energy directly into DNA. In direct damage, the energy is absorbed by the Compton Effect and photoelectric effect, and dominant high LET radiation, which can break single strands or double strands. Double-strand breaks usually result in cell death, while a single-strand break can normally be repaired by the cell [44, 45]. Indirect damage occurs when the free radicals are formed by energy transfer from radiation that interacts with DNA and causes cellular damage [46]. The cellular response to these damages includes complex repair mechanisms, mainly via processes of base excision repair, nucleotide excision repair, and homologous recombination [47].

Ionizing Radiation-Induced DNA damage and Insulin Resistance

Recent research suggests a relationship between DNA damage and insulin resistance, a precursor to type 2 Diabetes after exposure to ionizing radiation [48]. Previous studies showed severe insulin resistance after whole-body exposure to radiation in childhood [49]. DNA damage can result in oxidative stress and inflammatory reactions, both of which are known to contribute to insulin resistance. For example, oxidative damage brought on by radiation can trigger the release of pro-inflammatory cytokines like IL-6 and TNF-alpha as the activation of inflammatory pathways. Peripheral tissues may become less sensitive to insulin because of cytokines' ability to disrupt insulin signaling pathways [50, 51].

Ionizing Radiation Impact on Pancreatic Beta Cells

The immune system in type-1 diabetes attacks insulin-producing cells (beta cells) in the pancreas. Radiation may increase the risk of autoimmune conditions by damaging these cells or altering immune system regulation, triggering an autoimmune response [52]. The pancreatic beta cells, which are responsible for insulin production, are particularly susceptible to radiation-related damage [53]. These cells may experience direct DNA damage and subsequent apoptosis or dysfunction due to ionizing radiation exposure [54]. Experimental studies have shown that radiation can impair the function and survival of beta cells, impair

insulin secretion, and contribute to the development of diabetes [55]. In addition, radiation-induced damage to the pancreatic microenvironment may further exacerbate beta-cell dysfunction [56]. Another study indicated that radiation exposure to the tail of the pancreas is significantly associated with a higher risk of diabetes, with this risk closely linked to the radiation dose [57]. In contrast, radiation to other areas of the pancreas did not show a connection to diabetes risk [58]. While the mechanisms behind ionizing radiation-induced diabetes are not completely understood, it is suggested that damage to specific β-cells and insulin secretion may contribute to this risk in cancer survivors [59].

Ionizing Radiation-Induced Diabetes

A prior study found a link between abdominal or total body irradiation and an increased risk of diabetes [60, 61]. Several studies indicated that cancer survivors with diabetes mellitus, particularly type 2, have a two-fold higher risk if they underwent radiation therapy for Wilms tumor, acute myeloid leukemia, neuroblastoma, or Hodgkin lymphoma. Additionally, survivors of brain tumors and acute lymphoblastic leukemia face a higher risk of obesity in adulthood. Overall, cancer survivors are more likely to develop diabetes than their siblings, especially those who received abdominal radiotherapy or total body irradiation during childhood cancer treatment [62, 63]. This association with Hodgkin's lymphoma treatment and an elevated risk of diabetes has been confirmed [64]. Recent research has suggested that low-dose (0.5 Gy) ionizing radiation may actually help prevent the onset of diabetes mellitus. Possible mechanisms include the induction of antioxidants in the pancreas, protection of β-cells from oxidative damage, and immunomodulation that supports pancreatic function [65]. Diabetes is a disease that results from hyperglycemia and leads to a disorder of cellular metabolism [66]. The impaired metabolism causes oxidative stress and increases diabetes-related complications such as neuropathy, nephropathy, retinopathy, and coronary artery disease. Furthermore, the increased oxidative stress may impair β-cell function and promote insulin resistance, increasing the severity of diabetes [67].

Radiation Therapy and Diabetes Risk

The radiation could potentially cause breaks in the double helix or mutations. If mutations affect genes associated with diabetes, such as those controlling insulin production or glucose

metabolism (e.g., INS, HNF1A, or PPARγ), it could disrupt normal cellular functions. This disruption could potentially contribute to the onset of diabetes or worsen pre-existing conditions [68, 69].

Ionizing radiation can trigger epigenetic changes, such as DNA methylation or histone modification, which can influence gene expression. These changes can lead to the dysregulation of genes involved in glucose metabolism, insulin signalling, and inflammation, potentially impacting the development of conditions like type 1 or type 2 Diabetes [70, 71].

Oxidative stress from radiation can produce reactive oxygen species (ROS), leading to damage to cellular components, including DNA. This stress can result in mitochondrial dysfunction, insulin resistance, and inflammation, which are associated with the development of diabetes [72].

Specific gene-environment interactions, such as TCF7L2, may increase susceptibility to type 2 Diabetes. Radiation exposure could interact with genetic predisposition, potentially increasing the risk of developing diabetes in genetically susceptible individuals [73].

Radiation can activate inflammation and immune system responses, which may impact the pancreas or other organs. Chronic inflammation is a recognized risk factor for insulin resistance and diabetes. The Effects of Radiation Therapy in Individuals undergoing radiation therapy (e.g., cancer treatment) may expose nearby organs like the pancreas to radiation, raising the risk of developing diabetes as a long-term side effect [74-76].

Cancer patients receiving radiation therapy may face a higher risk of developing diabetes [77]. Various studies of childhood Hodgkin lymphoma and cancer survivors have reported that infra-diaphragmatic radiotherapy may increase the hazard of diabetes [78, 79]. Research shows that radiation therapy, particularly when targeted to the abdominal or pelvic regions, can negatively affect insulin sensitivity and glucose metabolism [80-82].

This effect is partly due to radiation-induced damage to pancreatic tissue and surrounding vascular structures [83, 84]. Long-term survivors of radiation therapy often demonstrate altered glucose homeostasis, highlighting the need for monitoring and managing diabetes risk in these populations [85, 86].

Preventive Measures and Management

Given the potential connection between radiation-induced DNA damage and diabetes, prevention and control techniques are critical. For individuals undergoing radiation therapy, dose optimization and planning can help minimize exposure to non-target tissues, including the pancreas. Regular glucose level monitoring and early intervention techniques such as lifestyle changes and pharmacological treatments can effectively reduce the hazard of diabetes.

Conclusion

Radiation-induced DNA damage has a variety of impacts on the risk of diabetes, influencing both the development of direct damage to pancreatic beta cells and insulin resistance. Although the exact mechanisms are still being elucidated, it is evident that radiation exposure is a significant risk factor for diabetes, especially in populations with high levels of radiation exposure and cancer survivors. Further study is required to understand this relation and to develop targeted interventions to reduce diabetes hazards in impacted populations. Diabetes mellitus, a chronic metabolic condition defined by high blood glucose levels, can be caused by a variety of hereditary and environmental causes. Recent research has begun to highlight how radiation-induced DNA damage may interact with these variables to aggravate or perhaps initiate the pathogenesis of diabetes. This junction is relevant in the context of cancer survivors who have had radiation therapy, as they have a higher risk of developing type 2 Diabetes.

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