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THE ANALYSIS STUDY OF ASSOCIATION OF TYPE 2 DIABETES MELLITUS AND SKIN CANCER : A COMPREHENSIVE SYSTEMATIC REVIEW

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ABSTRACT

Background: *The correlation between type 2 diabetes and skin cancer has been established, with elevated blood glucose levels and increased insulin levels associated with a higher risk of certain malignancies, such as nonmelanoma skin cancer. However, the impact of insulin therapy on cancer risk in individuals with type 2 diabetes is generally not significant. Understanding this correlation can help develop effective strategies for managing both conditions.*

Methods: *Following PRISMA 2020 guidelines, this systematic review concentrated on full-text English literature published between 2014 and 2024. Editorials and review articles that appeared in the same journal as the submission were not accepted without a DOI. A number of websites, including ScienceDirect, PubMed, and SagePub, were utilized to gather the literature.*

Result: *The study looked at more than 100 publications using reputable sources including Science Direct, SagePub, and PubMed. After it was decided that eight publications needed greater investigation, a more extensive review of the entire literature was carried out.*

Conclusion: *The incidence of skin cancer in diabetic individuals is higher in those aged 60 and older, with males more likely to develop non-melanoma skin cancer (NMSC) and melanoma. Risk factors include sex, comorbidities, immunosuppression status, and socioeconomic status. Insulin therapy can lower the risk of NMSC, but further studies are needed to understand differences in incidence.*

Keyword: *Diabetes, skin cancer, correlation, incidence, NMSC*

INTRODUCTION

Diabetes has the potential to cause major systemic complications over time that raise morbidity and mortality considerably. Elevated blood glucose levels are a hallmark of diabetes, a chronic medical condition.[1] It has become a burden on the socioeconomic structure and poses a threat to public health.[2] Research has found that individuals with diabetes mellitus (DM) face a higher risk of developing certain cancers, such as those affecting the liver, biliary tract, pancreas, stomach, colorectum, kidney, bladder, breast, and endometrium, but a lower risk of developing prostate cancer.[3,4] Some studies have established a connection between diabetes and the development of specific malignancies, such as nonmelanoma skin cancer (NMSC).[5,6] Based on retrospective cohort studies conducted in Taiwan and England, people with diabetes who are 60 years of age or older are more likely to develop non-motor stroke (NMSC).[5] Similar to this, record linkage studies have demonstrated a link between diabetes-related hospitalization and an increased risk of different cancer types, including NMSC.[6]

Recently, there has been speculation that cancer development in diabetic patients may be influenced by persistent high blood sugar and increased levels of insulin or insulin-like growth factor (IGF). The presence of persistent high blood sugar may promote the overproduction of reactive oxygen species and superoxide, as well as the growth of cancer cells.[7] Studies have shown that IGF plays a role in modulating the proliferation of epidermal cells. Moreover, high levels of insulin and IGFs in individuals with diabetes have been associated with increased cellular proliferation, activation of oncogenic epidermal growth factor receptors, and subsequent promotion of malignant cell transformation.[7,8] Various observational randomized trials have been conducted to explore the potential link between insulin therapy in diabetic individuals and the risk of cancer. The findings have been mixed, with some suggesting a heightened cancer risk associated with insulin therapy and others finding no such association. These contradicting findings might be a reflection of cancer's biological variability. On the other hand, most epidemiological research refutes the notion that insulin therapy significantly lowers the risk of cancer in people with type 2 diabetes.[9] Other trials, such as the ORIGIN trial, have not found any increased risk of any particular cancer types, such as lung, breast, prostate, colorectal, or melanoma, associated with insulin therapy, despite the DIGAMI trial's indication of a correlation between the medication and higher cancer mortality.[1]

Melanoma and nonmelanoma skin cancer, which includes squamous cell carcinoma, basal cell carcinoma, and malignant neoplasm of the sweat and sebaceous glands, are the two main types of skin cancer. These were some of Taiwan's top ten most prevalent cancer types.[10,11] The most prevalent type of cancer in humans, non-melanoma skin cancer has significantly increased in incidence, morbidity, and associated treatment costs globally over the past few decades.[12] This type of skin cancer usually manifests as a lump or discolored patch that slowly grows in the top layers of the skin after being exposed to the sun. According to estimates from the World Health Organization (WHO), there are two to three million new cases of non-motor stroke cases diagnosed globally each year. NMSC is one of the most prevalent cancers in North America, particularly in older White men.[1] Since its prevalence and incidence rate have been steadily rising over the past three decades, NMSC has become recognized as a significant public health issue of international concern. The primary risk factors for non-malignant solar cell carcinoma (NMSC) are fair skin, a history of sun damage, and prolonged exposure to ultraviolet (UV), particularly ultraviolet B (UVB) radiation.[1]

In addition, the Disability-Adjusted Life Years (DALYs) for NMSC increase exponentially with age, according to the Global Burden of Disease Study (1990–2017). In general, it is discovered that men experience NMSC at a higher rate than women.[13] Additionally, the results of meta-analyses indicate a connection between alcohol use and a higher risk of NMSC as well as a relationship between BMI and NMSC. As a final point, despite the fact that smoking has been consistently associated with a number of cancer types, there is evidence that current smoking is associated with a lower risk of NSMC.[1] However, there hasn't been much research done on DM patients' risk of developing skin cancer. Epidemiological studies conducted in other nations have shown varying correlations between malignant melanoma or NMSC and type 2 diabetes, with relatively few reports describing the relationship between NMSC and DM.[5] Comprehending the correlation between type 2 diabetes mellitus and skin cancer can facilitate the development of efficacious strategies for managing both ailments. This systematic review, which was based on studies done over the previous ten years, sought to investigate the connection between type 2 diabetes mellitus and skin cancer.

METHODS

PROTOCOL

The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 standards were closely followed by the study's author to ensure compliance with all regulations. To provide accurate and persuasive research findings, a well-considered approach was used.

CRITERIA FOR ELIGIBILITY

An extensive review of research on the relationship between type 2 diabetes mellitus and skin cancer undertaken during the last ten years is given in this study. By means of comprehensive data analysis, this program aims at clarifying and improving patient care protocols. This thesis' main goal is to highlight important subjects that are covered in a range of literary works.

Strict inclusion and exclusion criteria were applied in order to guarantee the accuracy of the data used in this analysis. All works released in English between 2014 and 2024 are acceptable for inclusion. Public reviews, editorials, submissions without a DOI, and multiple entries in the same publication are among the exclusion criteria.

SEARCH STRATEGY

The study's keywords include "diabetes mellitus, type 2 diabetes mellitus, DM, T2DM, skin cancer, relationship, risk factor, outcomes and prognosis". For this research, the following Boolean MeSH keywords were entered into the databases: (((“diabetes mellitus”[MeSH Terms] OR “type 2 diabetes mellitus“[All Fields] AND “skin cancer”[All Fields]) OR (“DM OA”[MeSH Terms] OR “T2DM”[All Fields] AND “skin cancer”[All Fields]) AND (“asssociation”[MeSH Terms] OR “cancer”[All Fields] OR “relationship”[All Fields] OR “risk factor”[MeSH Subheading] OR “outcomes”[All Fields] OR “prognosis”[All Fields]))).

DATA RETRIEVAL

The authors carefully considered the relevance of each article based on its title and abstract before starting this extensive investigation. More weight was only given to studies that satisfied the inclusion and goal criteria of the article. After several searches, a distinct and dependable pattern became apparent. The only language in which full-text submissions were accepted was English. Content that directly related to the study's topic and met all predetermined inclusion criteria was produced by the most stringent screening process. Studies that did not meet these standards were typically ignored, and their conclusions were not given much weight. Numerous pieces of information were included in the evaluation, such as factors, titles, authors, publication dates, locations, and study procedures.

QUALITY ASSESSMENT AND DATA SYNTHESIS

The writers themselves carefully review the abstract and title of each article to decide which ones need more research. Every document that was initially available for review had to be carefully examined after that. The review papers were chosen using the evaluation results as a guide. This criterion allowed papers to be selected for additional analysis more quickly, which in turn allowed for a more thorough assessment of previous research and the conditions surrounding its evaluation.

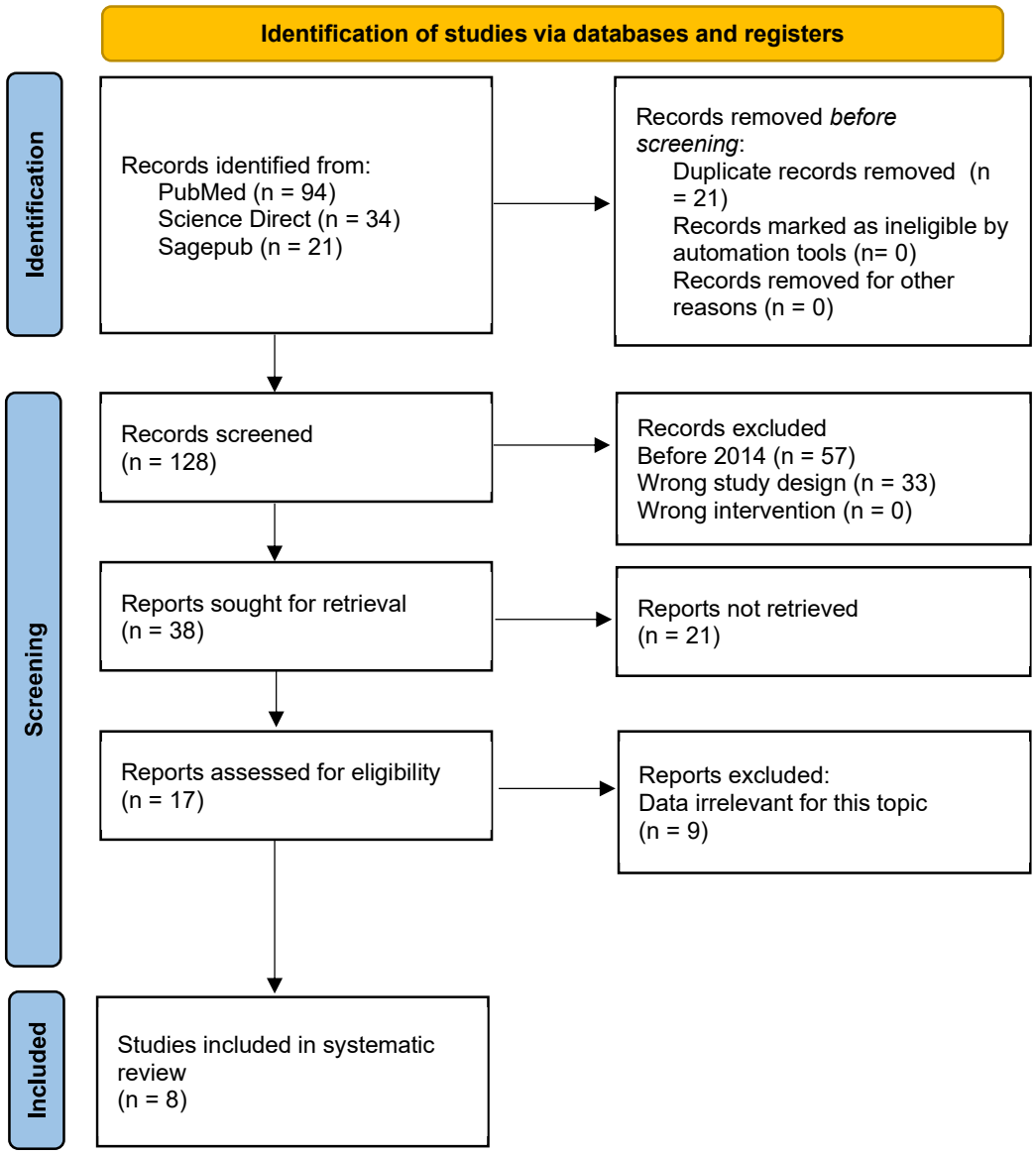

Figure 1. Article search flow chart

RESULT

Our team started the investigation by meticulously compiling a substantial collection of publications from reliable sources including Science Direct, PubMed, and SagePub. We picked eight papers that were deemed extremely relevant to our current systematic investigation after a rigorous three-stage screening process. Following that, we narrowed down certain subjects for more study and carefully assessed each report. To help you speed our investigation, we have provided a brief overview of the assessed content in Table 1.

Table 1. The literature included in this study

Author	Origin	Method	Sample	Result
Tseng et al.[5] (2016)	Taiwan	Retrospective Cohort	41.898 patients	Skin cancer risk is significantly higher in older adults with diabetes mellitus (DM), with factors such as immunosuppression status, sex, comorbidities, and immunosuppression status contributing to the risk. Factors such as older males, chronic obstructive

				pulmonary disease, and coronary artery disease for melanoma also contribute to the risk. The incidence rate and risk of skin cancer are higher in older adults with DM.
Tang et al.[14] (2018)	USA	Meta Analysis	21 studies	The study found no significant increase in melanoma risk among SGLT2 inhibitor users, and no significant difference in non-melanoma skin cancer risk. However, a decreased risk was observed among trials with duration < 52 weeks. Current evidence from RCTs does not support a significant increased risk of skin cancer associated with SGLT2 inhibitors.
Lyundup et al.[15] (2022)	Russia	Systematic Review	28 studies	The study found that initial diabetic foot ulcer (DFU) misdiagnosis is linked to patient age, gender, and wound duration. Lesions misdiagnosed as DFU are often mistaken for other cancers, with older patients having a 145% higher risk of suspicion. Clinicians should be aware of potentially malignant foot lesions in elderly patients with diabetes.
Nwabudike et al.[16] (2021)	Romania	Case Report	-	A 75-year-old diabetic man with a history of right heel ulcers was diagnosed with malignant melanoma. Despite various therapies, delayed healing was observed. Diabetic foot ulcers are a common complication of diabetes, and prompt diagnosis is crucial for adequate treatment. A multidisciplinary approach, including dermatology consultations, is essential for successful treatment.
Pradhan et al.[17] (2023)	Canada	Cohort	514.706 patients	DPP-4 inhibitors were found to reduce the risk of melanoma by 23% compared to sulfonylureas, with the risk decreasing with longer use duration. However, these drugs were not linked to non-melanoma skin cancer incidence compared to sulfonylureas, with a higher incidence of non-melanoma skin cancer.

Ren et al.[18] (2023)	China	Case Report	-	A 56-year-old Asian male with type 2 diabetes and a history of chronic HBV infection was identified as having MCC, which is characterized by lymphovascular invasion and involvement of the parotid gland, muscle, nerve, and adipose tissue. He received split-thickness skin grafting, neck lymphadenectomy, parotidectomy, and extensive resection.
Massouh et al.[1] (2024)	Lebanon	Retrospective Study	8.685 patients	According to the study, insulin users had a much higher chance of having an NMSC event-free survival than diabetic patients who did not take the medication. Along with indices of SDOH, insulin use also decreased hazard and the likelihood of NMSC.
Pradhan et al.[19] (2024)	Canada	Cohort Study	220.000 patients	There was no observed increase in the risk of either nonmelanoma or melanoma skin cancer when using GLP-1 RAs. Secondary and sensitivity analyses produced consistent results, and there was no indication of a cumulative duration of use association.

Nwabudike et al. and Lyundup's studies highlight the importance of prompt diagnosis in providing adequate treatment for diabetic foot ulcers. Tseng's study found a 1.18 times higher incidence of skin cancer in diabetic patients compared to non-DM cohorts, with a 1.46 times higher risk after adjusting for sex, comorbidities, and immunosuppression status. Tang et al. found no significant association between SGLT2 inhibitors and NMSC risk, but a decreased risk observed among trials with duration < 52 weeks. Nwabudike et al. emphasize the need for a multidisciplinary approach to foot ulcer therapy, emphasizing the need for a comprehensive approach to prevent skin cancer.

Pradhan et al.'s 2023 study found that DPP-4 inhibitor users were more likely to be obese, have longer diabetes duration, and have microvascular diseases. The use of DPP-4 inhibitors was associated with a 23% decrease in melanoma incidence compared to sulfonylureas. According to Ren et al., MCC is an aggressive, uncommon skin cancer that typically affects older White people. Insulin use was found to have a significant correlation with SDOH and other variables, and to shorten the time-to-diagnosis with NMSC in diabetic participants.

DISCUSSION

The emergence of aggressive neuroendocrine skin cancer has been linked to diabetes mellitus, a common chronic inflammatory illness.[19] When comparing diabetic (DM) individuals to non-DM cohorts, skin cancer incidence is higher in DM individuals 60 years of age and older. Risk factors for skin cancer in diabetic individuals include sex, comorbidities, and immunosuppression status. Males are more likely to develop skin cancer, non-melanoma skin cancer (NMSC), and melanoma, while chronic obstructive pulmonary disease (COPD) and coronary artery disease (CAD) are also significant risk factors. Since 2000, skin cancer has been one of the top 10 leading cancers in Taiwan.[5] According to research, people with diabetes who take insulin have a 44% lower chance of developing NMSC than people who do not take insulin. It has been demonstrated that insulin therapy in diabetic patients reduces the risk of developing NMSC, with the protective effect increasing with age. However, it is currently unclear which precise molecular and mechanistic pathways insulin therapy uses to lower the risk of developing NMSC in people with diabetes.[1]

The biological and behavioral results linked to insulin use and diabetes management are directly impacted by a number of factors, including socioeconomic status, race, cultural and social factors, access to healthcare, and disparities in living and working environments. Age and higher income levels are strongly linked to higher odds of NMSC and lower insulin use percentages. Compared to White participants, Black participants have a lower risk of NMSC and a higher prevalence of insulin use.[20] Higher education levels are also linked to a higher risk of developing NMSC, potentially as a result of improved access to health information and knowledge of prevention techniques. On the other hand, a lack of knowledge about the early warning signs and symptoms of skin cancer, as well as missed opportunities for skin examinations, have all been associated with lower levels of education.[21] The relationship between diabetes and skin cancer is complex, and further studies are needed to understand the differences in the incidence of NMSC and melanoma between diabetic and non-diabetic cohorts.[5]

The meta-analysis found that SGLT2 inhibitors were not significantly associated with an increased risk of melanoma in patients with Type 2 Diabetes. However, the potential for harm was not entirely ruled out. A non-significant decrease in the risk of NMSC was observed, while a significantly decreased risk was detected in trials with a duration of < 52 weeks.[14] The opposite trend was observed for NMSC risk, indicating that SGLT2 inhibitors may not be photosensitizers that increase melanoma risk through phototoxicity. The study had several limitations, including reporting bias, a small number of skin cancer cases, and short-term follow-up. Future large prospective observational studies and post-marketing surveillance are needed to further assess the potential melanoma risk by SGLT2 inhibitors. In conclusion, current evidence from randomized trials did not find a significantly increased risk of skin cancer among type 2 diabetic patients taking SGLT2 inhibitors.[14]

This population-based cohort study found that DPP-4 inhibitors were associated with a reduced risk of melanoma compared to sulfonylureas, with evidence of a duration-response relationship. However, these drugs were not associated with non-melanoma skin cancer.[17] The DPP-4 enzyme plays a complex role in the malignant transformation of melanocytes, and biological findings in murine models explain its possible benefits in melanoma.[22] The study found no consistent association between DPP-4 inhibitor use and non-melanoma skin cancer. The variable roles of DPP-4 and CXCR3 on keratinocytes might explain the relatively null association between DPP-4 inhibitors and non-melanoma skin cancer.[23] More research is needed to confirm these findings, given the high mortality associated with melanoma and the lack of preventive strategies related to this malignancy.[17]

According to a recent study, people with type 2 diabetes who take GLP-1 RAs, like liraglutide, do not have a higher risk of developing skin cancer. This is the first population-based cohort study to evaluate the relationship between GLP-1 RAs and the incidence of skin cancer.[19] The results were consistent across secondary and sensitivity analyses. The co-occurrence of skin cancer and diabetes poses a challenge for treating both conditions effectively.[24] While diabetes alone does not increase the risk of skin cancer, the combination of skin cancer and diabetes complicates the treatment of both conditions.[25] The study has a number of advantages, such as answering concerns expressed by regulatory bodies, making use of a population-based database that is representative of the people in the UK, and taking possible differential censoring into consideration. These results should reassure regulatory bodies and medical professionals about the safety of widely used medications.[19]

Merkel cell carcinoma (MCC) is an uncommon cancer, affecting 98% of white people and 81% of people with sun-exposed skin. People of Black, Asian, and Hispanic descent have a lower risk of developing MCC, with light-colored skin being a major risk factor.[26] Diabetes mellitus and other chronic inflammatory diseases, such as connective tissue disorders, can greatly increase the risk of MCC.[27] Endothelial cells rely on vascular endothelial growth factors (VEGF) as essential mitogens for angiogenesis and lymphangiogenesis. Diabetes pathogenesis is linked to toll-like receptors (TLRs). It is worthwhile to investigate the relationship between diabetes and MCC further. Sentinel lymph node biopsy, radiotherapy, and/or primary tumor extirpation are recommended forms of treatment for local/regional MCC. But as of yet, there is no known cure for metastatic MCC.[18]

A recent systematic review of clinical cases has found that elderly patients with diabetes are more likely to have skin cancer misdiagnosed as diabetic foot ulcers (DFU).[15] The study indicates that clinicians should be especially cautious when determining the cause of foot wounds in elderly patients with diabetes. This is important because foot ulcers are a common complication of diabetes, affecting about 6% of patients. In some cases, clinicians may initially mistake foot wounds as being related to diabetic complications rather than malignancies. Malignant tumors, especially melanoma, may not exhibit typical features and can closely resemble chronic or benign wounds, such as DFU.[15] Acral lentiginous melanoma, which is the least common form of melanoma, is often found in areas prone to pressure and trauma, coinciding with the locations of diabetic foot ulcers.[28,29] Misdiagnosis can lead to delayed diagnosis and a poorer prognosis, emphasizing the need for accurate identification and multidisciplinary care. The importance of proper diagnosis and treatment of DFU is underscored by a case study highlighting the need for differential diagnoses and interdisciplinary care in these cases.[16] The study suggests that further epidemiological research is needed to understand the true frequency of malignancies misdiagnosed as DFU.[1]

CONCLUSION

A chronic inflammatory disease called diabetes mellitus has been linked to the emergence of aggressive neuroendocrine skin cancer. Compared to cohorts without diabetes mellitus, skin cancer incidence is higher in diabetics 60 years of age and older. Risk factors for skin cancer in diabetic individuals include sex, comorbidities, and immunosuppression status. Males are more likely to develop skin cancer, non-melanoma skin cancer (NMSC), and melanoma, while chronic obstructive pulmonary disease (COPD) and coronary artery disease (CAD) are also significant risk factors. It has been demonstrated that insulin therapy in diabetic patients reduces the risk of developing non-motor state cerebri (NMSC), with the protective effect increasing with age. The biological and behavioral outcomes related to insulin use and diabetes management are directly impacted by a number of factors, including socioeconomic status, access to healthcare, cultural and social factors, race, and disparities in living and working environments. Further studies are needed to understand the differences in the incidence of NMSC and melanoma between diabetic and non-diabetic cohorts.

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