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A REVIEW ON ASSOCIATION OF LOWER LIMB COMPLICATIONS AND CANCER RISK RELATED TO TYPE 2 DIABETES:

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Abstract

Lower limb complications associated with diabetes are peripheral sensory neuropathy and peripheral artery diseases. Amputation risk increases with diabetes and mostly happens in the lower limb. Disabilities occur due to lower limb complications which then affect patients' health and social lives. Diabetes is associated with other diseases like cardiovascular issues, cancer, etc. Death risk in diabetes type 2 patients having lower limb complications is highly associated with cancer. When the interaction between peripheral neuropathy and peripheral artery diseases (PAD) with cancer death risk is measured, it showed a high association with PAD having a hazard ratio of 8.9 and peripheral neuropathy patients having a hazard ratio of 8.4. Among them, lower limb arterial thrombosis is highly associated with all cancer deaths. Lower-extremity complications are the leading cause of macrovascular and microvascular diseases. Other minor risk factors linked with lower limb complications are age, smoking, and obesity. The risk of lower limb complications and cancer is prevalent among smokers as compared to non-smokers. However, there is no particular study on this factor. Lower-limb malignancies are associated with many biological disorders like increased glycation end products, chronic inflammation, and oxidative stress. In one study, cancer risk was measured among various diabetic patients having lower limb complications. The results showed less cancer death risk among the group of patients having proper glucose level and blood pressure level controls. Among all the cancers affecting diabetic patients, almost 4% are melanoma which if misdiagnosed during early stages due to various reasons can lead to biopsy. Acral melanoma is usually misdiagnosed in up to 40% of cases. The purpose of a biopsy is the diagnosis of the problem as well as the prediction of the exact stage of melanoma.

INTRODUCTION:

Lower limb complications that are often present in diabetic patients are peripheral sensory neuropathy and peripheral artery disease (Boulton, Vileikyte, Ragnarson-Tennvall, & Apelqvist, 2005). These complications are considered the major reason for amputation of the lower extremity. Amputation risk is 8 times more common in diabetic patients as compared to nondiabetic patients (Johannesson *et al.,* 2009). Disabilities are majorly associated with lower-extremity complications. These disabilities impact the patients' health and affect societies making life quality worse (Kerr *et al.,* 2019). In recent decades, the healthcare system is much improved but the life span of diabetic patients with lower-limb problems have been dramatically reduced (J. Walsh, Hoffstad, Sullivan, & Margolis, 2016). Cardiovascular diseases cannot be completely attributed as the major cause of the premature death risk in diabetic patients and its associated lower-extremity complications. Problems other than cardiovascular issues might also be involved (Brownrigg *et al.,* 2014).

Cancer is a common public health issue around the world. It is also the second most common cause of death (Lozano *et al.,* 2012). Among various skin cancer types, about 4% are due to melanoma. While 79% of skin cancer deaths are due to melanoma. Diagnosis of melanoma becomes easy due to its early detection (Fortin, Freiberg, Rees, Sondak, & Johnson, 1995). According to recent data, the death risk of cancer is reported more among diabetic patients when compared to others (Rao Kondapally Seshasai *et al.,* 2011). Cancer risk is also related to the increased risk of cardiovascular diseases (Youn *et al.,* 2020). There are few studies on the evaluation of the death risk of cancer related to cardiovascular problems in diabetic patients but their reports show inconsistent findings. According to previous data available, an investigation into the association between cancer deaths and lower-extremity complications in diabetic patients has not been done (Wong *et al.,* 2012).

Association of Cancer with Lower limb complications in Diabetes Type 2:

Finding a relationship between lower limb complications in diabetic patients and cancer death risk is not quite simple as it is a multifactorial disorder. Not much data is available on it. In 2021, one ADVANCE study was done to find out the association between a history of lower limb complications and the cancer death risk. ADVANCE stands for Action in Diabetes and Vascular Disease: PreterAx and DiamicroN Modified-Release Controlled Evaluation. It was the huge multicenter international trial that was conducted to estimate the effects of intensive glucose control among Type 2 diabetes patients. The study was done on 11,140 patients belonging to Asia, Europe, and some other developed countries. This trial was done using treatment based on gliclazide-MR and blood pressure by giving a combination of fixed doses of indapamide and perindopril on the occurrence of macrovascular and microvascular events (Committee, 2001). Clinical parameters made for the study were participants of 66 years of age must have a diabetic history of 7.9 years (average) and a mean HbA1c value of 7.5. 38% of the participants had a history of lower-extremity complications at baseline of which 22% had PAD while 27% had peripheral neuropathy. While 10% of the total participants had a history of both peripheral neuropathy and PAD. Patients were divided into two groups. One group was treated with gliclazide to achieve an HbA1c of 6.5 or less. While, indapamide in combination with perindopril or a placebo was given to another group (Huisman, 2007). The results showed low cancer death risk among patients of the glucose control group as compared to other groups having a combination of glucose control or a placebo. Several trials were also performed to calculate the relation between other associated complications of diabetes and the cancer death risk. Findings from this study were reliable as it considered non-cancer causes of death as competing risks. Increased risk of cardiovascular and other cause deaths was linked to PAD and lower-extremity complications. However, peripheral neuropathy is only linked to all-cause deaths. The history of peripheral artery diseases was also related to the increased cancer incidence, specifically digestive and solid neoplasms (Mohammedi *et al.,* 2021).

Effect of Lower-extremity Complications on Cancer Death Risk:

The interaction of peripheral neuropathy and PAD was tested to check their association with death risk due to cancer in a recent study(Mohammedi *et al.,* 2021). Several sensitivity analyses had been performed to test the risk factors depending on the history of peripheral neuropathy, lower-extremity issues, or foot ulceration. Conditions such as palpation, absence of peripheral pulse, revascularization of the lower limb, and amputation of the lower limb are regarded as PAD. Sensory neuropathy is regarded as the occurrence of two neurological problems; a disturbance in the sensation of slight touch, absence of reflex in the knee or ankle, or chronic ulceration (Tesfaye *et al.,* 2010). It is reported that individuals having lower-extremity complications history, PAD, or peripheral neuropathy showed a greater incidence of deaths due to cancer as compared to patients without such complications (Mohammedi *et al.,* 2021).

Effects of other diabetes-associated problems:

Other diabetes-associated problems include coronary artery issues like coronary angioplasty, unstable angina history, myocardial infarction, and coronary artery bypass. Diabetes-related cerebrovascular complications include an attack of transient ischemia or stroke. A history of cardiovascular issues increases the death risk due to cancer among diabetic patients. The death rate is more among cardiac patients who had PAD or other lower limb complications. Retinopathy issues like macular odema, retinal laser therapy, proliferative retinopathy, and diabetes-associated blindness are regarded as diabetic retinopathy.

Effects of Smoking:
The association of cancer death risk and lower-limb issues has been evaluated between smokers and non-smokers. Although, smoking alone could not be regarded as a main risk factor for cancer death due to lower limb complications. The extent of this association was comparable as the analysis was performed between smokers and non-smokers. But there is a need for further investigation of the effects of smoking on the association of cancer deaths and lower-leg complications.

Biopsy for the diagnosis of foot ulcers:
Malignant melanoma is considered one of the severe cutaneous neoplasms of the skin. It is difficult to differentiate between less severe skin lesions and malignant melanoma. Diagnosis of melanoma becomes easy due to its early detection (Fortin, Freiberg, Rees, Sondak, & Johnson, 1995). But the rate of survival is less with initial foot melanoma. Melanoma is usually misdiagnosed due to its earlier poor prognosis (S. M. Walsh, Fisher, & Sage, 2003). Acral melanoma is most of the time misdiagnosed in up to 40% of its cases. Its location is usually less common due to which it is misdiagnosed and also it does not follow the changing mole pattern. It is usually ulcerated and amelanotic. But, pigmentation is often present in amelanotic melanoma (Bennett, Wasson, MacArthur, & McMillen, 1994). While, tinea pedis, pyogenic granules, blisters, benign naevi, foreign bodies, non-healing ulcers, and fungal infections are some other common misdiagnoses that have been reported. Prognosis by non-dermatologists is one of the reasons for delayed diagnosis and misdiagnosis *(Metzger et al.,* 1998). Lesions that are not painful are not considered by the physician and also by the patients (S. M. Walsh *et al.,* 2003). Accurate and early prediction of malignant melanoma is needed but it is difficult due to poor forecast of melanoma in its initial stages.

In the case of non-healing and atypical ulcers, a biopsy should be performed. The purpose of biopsy, preferably excisional biopsy, is not only to diagnose but also to know about the melanoma stage (John, Hayes Jr, Green, & Dickerson, 2000). A very small amount of tissues is used to perform biopsies for histological diagnoses. A biopsy of a suspicious lesion is necessary. There is about a 39% ratio of the misdiagnosis of malignant melanoma (Soon *et al.,* 2003). Cause of the majority of ulcers is usually unnoticed in patients due to ischemia or neuropathy and also due to both of them. Foot deformity also leads to an increase in disease risk. Despite continuing the medical management of a non-healing ulcer, a biopsy would be considered. If an ulcer appears suspicious and deep, a dermatologist should be consulted earlier. Prescribing the clinician decides about the biopsy of a foot ulcer (Kong *et al.,* 2008).

Discussion:
In 2021, an investigation into the association between cancer death risk and lower-leg complications was reported for the first time (Mohammedi *et al.,* 2021). In a previous study, increased cancer incidence was reported among patients with severe limb ischemia or intermittent claudication (Onega *et al.,* 2015). While another population-based study from Denmark reported the relationship between arterial thrombosis in the lower limb with the enhanced risk of cancers in 6600 patients (Sundbøll, Veres, Horvath-Puho, Adelborg, & Sørensen, 2018). A lower extremity arterial thrombosis was related to the increased risk of all-cause deaths following site-specific (particularly smoking-dependent) cancers.

A possible mechanism for the association of lower-extremity malignancies with cancer death:
These findings about the association of cancer death risk and lower limb issues do not guarantee the actual cause of cancer death risk. It only proposes that lower-limb malignancies may be a reason for the risk of cancer death. Lower-extremity complications are the leading cause of macrovascular and microvascular disease, which when prolongs results in other multisystem diseases. Some variable risk factors of lower-leg malignancies are age, tobacco smoking, and obesity (Torre *et al.,* 2015). But these findings of various associations could not be called the main risk factors. Lower-limb malignancies are also associated with other biological disorders like increased glycation end products, chronic inflammation, and oxidative stress (Barrera, 2012). DNA damage and lipid peroxidation are caused by oxidative stress, which then results in diseases like atherosclerosis, microvascular, and cancer (Mohammedi *et al.,* 2015). A lower limb impairment known as endothelial dysfunction is also associated with solid tumor cancer risk. Excessive angiogenesis which is caused due to endothelial metabolic defects is the main characteristic of cancer (Eelen *et al.,* 2018).

Effects of blood pressure and glucose control on death risk of cancer:
There are no reports about the association between the risk of cancer-caused deaths and the treatment of blood pressure (Stefansdottir *et al.,* 2011). But an association between intensive glucose control and the risk of cancer deaths is reported. In 2010, a study showed that the risk of cancer death is less in patients having glucose and blood pressure control as compared to those patients who were given typical glucose control and placebo treatment for blood pressure. This finding gives rise to a hypothesis that the possible effect of multi factors on the occurrence of cancer death in patients with type 2 diabetes. To test this hypothesis, random clinical trials should be set up (Lloyd-Jones *et al.,* 2010).

Conclusion and Future Prospects:
Recent data on the association between cancer death and lower limb complications among diabetes type 2 patients indicates that there is a relation between them. The presence of problems like PAD and sensory neuropathy increases the chances of cancer death among diabetic patients. It also showed that having a better glucose control level and attaining the normal level of HbA1c minimizes the death risk. However, there is still a need for more research on this. The association should be measured for blood pressure. Also, there is no such evidence of the effect of smoking and other

contributing factors like obesity, cardiovascular issues, etc. So these parameters should also be checked. There is also a need for awareness about lower limb complications and foot ulcers among diabetic patients so that early diagnosis of such complications can save lives.

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