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AN OVEVRIEW OF THE USE OF STATIN AND METFORMIN AMONG ELDERLY WOMEN WITH BREAST CANCER AND DIABETES

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Abstract:
The inverse correlation of the malignancies evaluated with metformin usage, demonstrated even after short durations of treatment, raises the hypothesis that the primary benefit is diabetes control rather than the pharmacological activity of this specific medication. Databases reviewed for all the relevant articles in literature published up to the end of 2021. Metformin may reduce the incidence of breast cancer, according to emerging evidence, however reports are varied and few include information on tumor features. Prediagnostic statin use, on the other hand, was found to predict lower death from breast cancer and other causes.

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INTRODUCTION:

Breast cancer is the most frequent cancer among females worldwide, in both industrialized and developing countries [1]. Different kinds of breast cancer account for 15% of all cancer deaths in women. Age, early menarche, late menopause, nulliparity, use of oral contraceptives, hormone replacement therapy, family history, and obesity have all been recognized as risk factors for breast cancer [2]. People with type 2 diabetes (T2D) are also more likely to develop breast cancer [3, 4].

Metformin is a frequent first-line oral treatment for type 2 diabetes. Metformin has been suggested to reduce the incidence of breast cancer over the years, however a meta-analysis found inadequate evidence to support this idea [6]. Metformin has been proven in numerous preclinical investigations to have anticancer effects in both breast cancer and other forms of cancer [7]. The insulin/insulin-like growth factor-1 signaling pathway and the adenosine monophosphate-activated protein kinase (AMPK) pathway are recognized to be linked cancer-growth pathways. AMPK inhibits cancer proliferation and growth by adversely regulating the mTOR (mammalian target of rapamycin) signaling pathway [7]. The precise mechanics are unknown. Furthermore, it has been reported that the usage of glargine (a long-acting insulin analogue used in diabetic patients) is linked to an increased risk of breast cancer [8].

Statins, or 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, are among the most widely used cholesterol-lowering medications worldwide. Mevalonate reduction with statins is related with cancer cell apoptosis [9]. In vitro, lipophilic statins appear to inhibit tumor-cell growth and survival [10]. However, a meta-analysis found no link between statin use and breast cancer incidence in the general population, despite the fact that women with T2D were not analyzed separately in this investigation [11].

Several epidemiological studies have shown support for the effect of these medicines on breast cancer outcomes, despite a growing body of scientific evidence supporting a potential role of insulin, metformin, and statin in the progression of breast cancer [12]. Exogenous insulin, for example, was related with a worse survival rate, but metformin, a biguanide used as a first-line treatment for type II diabetic mellitus (DM), was associated with a higher survival rate in patients with both breast cancer and DM [13]. The usage of statins, the most commonly used cholesterol-lowering medicine family for CVD prophylaxis, has also been linked to a lower risk of breast cancer recurrence and mortality [14]. Surprisingly, some of those studies revealed a link between metformin or statin use and improved clinical outcome in a specific subtype of breast cancer, such as HER2-positive or estrogen receptor (ER)-positive tumors [13].

However, past clinical study outcomes have been contradictory, and interpretation of these research is frequently restricted by small sample sizes and patient heterogeneity [14]. Furthermore, several of them failed to account for stages and disease subtypes, which are known to be extremely related to the prognosis of breast cancer patients. Furthermore, the majority of previous research on this topic were conducted in Western countries, with only a few conducted in Asia, and the findings from Western populations may not be immediately applicable to Asian patients [15].

DISCUSSION:

Diabetes mellitus is a common illness that has been linked to an increased incidence of breast cancer, a result that has lately been disputed by large population-based studies [15]. Nonetheless, diabetes has been associated to a poor result in breast cancer patients. A meta-analysis7, as well as two recent investigations [6,7], discovered that individuals with breast cancer and diabetes had considerably higher all-cause mortality than those who did not have diabetes. Furthermore, all patients with breast cancer who have greater fasting insulin levels, higher levels of C-peptide (a marker of insulin production), or enhanced insulin resistance as measured by the homeostasis model assessment (HOMA) score are at a higher risk of dying from the disease [10,15].

Metformin is a biguanide that is extensively used to treat type 2 diabetes. It improves glycemic control and increases insulin sensitivity. Metformin has been explored for anticancer benefits based on these features and preclinical evidence of its suppression of breast cancer growth [16].

Following early reports, a meta-analysis of observational studies in individuals with type 2 diabetes found that metformin use was associated with a 30% lower overall incidence of cancer compared to patients with diabetes receiving other therapies, and a 44% lower cancer mortality compared to an age-matched general population in a cohort study. Although some observational studies show a decreased incidence of breast cancer when metformin

is used, the results are mixed, and data on breast cancer subtypes is limited [17,18].

Insulin promotes cell growth while decreasing apoptosis. Type 2 diabetics have greater levels of circulating insulin (and a higher risk of incident breast cancer than nondiabetic women [19]. Insulin receptors are present in untransformed at-risk breast epithelial cells, implying that insulin modulation may influence breast cancer risk. Metformin is a well-tolerated biguanide drug used to lower diabetic patients' circulating insulin levels. It inhibits glucose production in hepatocytes and may also inhibit protein synthesis and proliferation in at-risk epithelial cells. Metformin lowers high insulin levels in diabetic patients as a side effect [19]. Metformin reduces the level of circulating insulin in diabetic patients and may slow the rate of cell proliferation in epithelial cells, lowering the risk of breast cancer [20]. Adenocarcinomas were four times more common in untreated mice than in mice treated with phenformin, a biguanide comparable to metformin that was removed from clinical usage in the 1970s due to side effects [20]. Metformin's influence on breast cancer risk has been studied in three observational studies [21]. Two European cohort studies looked at total cancer risk as their primary endpoint and then looked at breast cancer risk. The first study found that Scottish women with their first metformin prescription (N 14 3,723) had a 40% reduced risk of breast cancer than those with no record of metformin prescription, although only 24 breast cancer cases were exposed to metformin [22]. A second study, conducted in The Health Information Network, a subset of the United Kingdom General Practice Database (N 14 27,654), found no significant association between any antidiabetic treatment—sulfonylureas, sulfonylureas plus metformin, and insulin (Hazard Ratio 14 0.90, 0.98, and 1.07, respectively)—and incident breast cancer risk compared to metformin only users [23]. Uncontrolled confounding by breast cancer predictors such as menopausal status, parity, and age after first birth was present. A recent case-control study using the UK General Practice Database (N 14 1,458) found no overall association between metformin use and breast cancer risk, but it did find a 56% lower risk of breast cancer associated with long-term metformin use (5 years) compared to other antidiabetic medication use. This inverse connection, however, was based on only 17 exposed breast cancer patients [19].

The above observation is most likely multifactorial in nature. First, in the current studies, cardiovascular mortality may have contributed to an increase in all-cause mortality with exogenous insulin or statin treatment. As the survival of patients with early stage and metastatic breast cancer has improved, cardiovascular death has become a clinically relevant cause of mortality [13,17]. Recent investigations on a Western population identified older age at diagnosis, CVD history, and the number of cardiovascular risk variables as risk factors for cardiovascular death in breast cancer patients. Indeed, insulin is typically provided for individuals with long-standing or poorly controlled diabetes, whereas statins are typically taken for those with existing CVD or at high risk for CVD [22].

Furthermore, exposure to insulin, metformin, or statin could have influenced breast cancer mortality via the pharmacological effects of the examined medicines on breast cancer. Numerous preclinical studies have been conducted to investigate the probable mechanisms causing these effects. With insulin resistance and hyperinsulinemia connected to a poor prognosis in individuals with breast cancer and diabetes [24], Chappell et al. [25] proposed that insulin has a direct mitogenic action via its receptor. Insulin has also been demonstrated to inhibit the expression of insulin growth factor- and sex hormone-binding proteins, resulting in an increase in active mitogens in the blood [25]. Metformin, on the other hand, inhibits mTOR signaling at the cellular level by activating AMP-activated protein kinase (AMPK) and reduces circulating insulin, leptin, and inflammatory marker levels systemically to exert its anticancer effects. Statins are thought to limit tumor growth directly by blocking the mevalonate pathway in cancer cells and indirectly by lowering systemic cholesterol levels, which can otherwise be used for tumor proliferation [19].

Patients exposed to metformin may be thought to reflect those with DM for a short period of time because metformin, as opposed to insulin, is often the first-line treatment for newly diagnosed diabetic patients [21]. Several features of our findings, however, cannot be totally attributed to confounding by such indications: the effect of insulin was partially negated by metformin administration, and metformin had variable actions depending on the tumor's hormone receptor positivity. There have been studies that support the biological plausibility of metformin's improved effect against ER-negative breast cancer. Metformin induced distinct apoptotic effects against triple-negative breast cancer cell lines via poly(ADP-ribose) polymerase cleavage, activation of caspase signaling cascades, and downregulation of epidermal growth factor receptor signaling beyond mTOR and AMPK, according to Liu et al. [26].

Given its ostensibly preventive effect against breast cancer, it may appear contradictory that statin users had a higher risk of death than non-users in our study. However, this is likely due to the statin's indication rather than its activity. Statin use can be indicative of an increased risk of cardiovascular mortality because statins are prescribed for people who have a higher risk of dying from CVD. Interestingly, the increase in all-cause mortality linked with statin use was greater with ER-positive disease than with ER-negative disease, implying that statins have an anticancer impact against ER-negative disease. Preclinical statin investigations on breast cancer found that ER-negative tumor subtypes were more responsive to statin treatment's anti-proliferative impact [26].

Prior observational studies have consistently linked diabetes to an increased risk of breast cancer. This connection, however, has lately been called into question in two large population-based cohort studies [4,5]. The British Columbia Linked Health Database, which covers 99% of the province's 4.8 million citizens, was utilized to produce a retrospective cohort in the first study. Breast cancer incidence was not linked with diabetes status in a study of 2,381 participants (HR, 1.01; 95% CI, 0.92 to 1.10; P =.88) [5]. The Danish National Diabetes Register and Cancer Registry were linked in the second study to undertake cohort studies on the whole Danish population. Although the incidence of various malignancies, including those of the liver, pancreas, and lung, was substantially linked with diabetes in that scenario, the incidence of breast cancer was not (P =.37) [4]. Furthermore, time-varying studies revealed indications of potential detection bias, implying greater cancer surveillance immediately after diabetes diagnosis [4,5].

Until recently, observational studies [19,20] on metformin use and the risk of breast cancer were scarce and contradictory, with two of four studies indicating a significantly decreased incidence of breast cancer in women with diabetes who took metformin. Ruitter et al [21] recently published results from analyses that employed the Dutch National Medical Register (a drug-dispensing database) to create a cohort of 85,289 women. In this environment, women who used metformin had a statistically significantly lower incidence of breast cancer than those who used sulfonylurea derivatives (HR, 0.95; 95% CI, 0.91 to 0.98) [21].
Diabetes is associated with a more advanced stage of breast cancer in women. However, many studies, but not all, indicate reduced mammographic screening rates in diabetic women. Mammograms were required as part of the protocol in the WHI clinical trials. As a result, mammography frequency was equivalent in women with and without diabetes, and there was no significant difference in cancer stage between women with diabetes who did not use metformin and women without diabetes. Women with diabetes who used metformin had a somewhat higher frequency of mammography than nonusers. Metformin nonusers were more likely to be getting insulin and thus more likely to be seeking specialized care. Because specialist care providers are said to be less inclined to prescribe screening procedures, there may be a difference in screening. In any case, results were corrected for the frequency of mammography [27,28]. Clinical studies also support metformin's anti-cancer effect. Women without diabetes with invasive breast cancer who were randomly assigned to metformin for 2 weeks exhibited lower Ki-67, a marker of tumor proliferation, compared to nonusers in a preoperative research. Patients with breast cancer who had diabetes and used metformin had a higher frequency of full response (24%) than patients with diabetes who did not use metformin (8%) and patients without diabetes (16%; P =.02) in a retrospective neoadjuvant therapy analysis [29]. Finally, in retrospective studies, patients with diabetes and HER2-positive breast cancer who used metformin outperformed nonusers. Metformin use was not related with increased survival in patients with triple-negative breast cancer in post-hoc analysis in an adjuvant setting, however there was a trend for lower distant recurrence compared to women without diabetes [30].

Metformin use was also linked to a lower incidence of malignancies in multiple places such as the breast, colon, and others in population studies, which was not shown with other anti-hypoglycemic medicines. Others, on the other hand, report no evidence of reduced risk [30]. Metformin has also been tried therapeutically for the treatment of breast cancer, and various morphological and molecular changes have been seen [30]. Colorectal cancer survival improvements have been documented among diabetic Metformin users. Other investigations found a decreased rate of adenoma production and a lower rate of colonic adenoma recurrence. Given the strong mechanistic rationale for metformin's potential risk-lowering effect, as well as the somewhat inconsistent results of association studies of metformin use and cancer incidence, we investigated this relationship further in two large-scale, methodologically robust population-based case-control studies [31].

Bodmer et al. discovered a 56% reduction in breast cancer risk for women who had used metformin for 5

years or more compared to nonmetformin users, but a null to weak connection with less years of use. Other studies found that women who used metformin for 5 years or more had a lower risk of breast cancer, whereas short-term users did not. Their findings, which demonstrated no connection between metformin use versus sulfonylurea use alone and breast cancer risk, may be explained by discrepancies in exposure criteria [32].

The availability of comprehensive national records is a major strength of our study. The data quality in Finnish national registers, such as the Hospital Discharge Register, is judged to be high. Furthermore, the Finnish Cause of Death Register processes and procedures appear to respond adequately to the coding of causes of death for mortality data [33]. Furthermore, the Finnish Cancer Registry (FCR) contains information on practically all cancer cases in Finland, with 93% of cases microscopically verified. All Nordic Cancer Registries have demonstrated a high level of quality in terms of the completeness and correctness of the recorded data, and the causes of death of patients are obtained from national cause-of-death registries in all Nordic cancer registries. In comparison to other cancer registries, the Finnish Cancer Registry reassesses cancer fatalities alongside registry incidence data [33].

The biggest limitation of our study is that we only have information from the registrations. Traditional prognostic variables and particular subtypes of breast cancer, such as hormone receptor status, are not included in the registers. Nelson et al. [34] proposed in a preclinical research that statins may be more effective in oestrogen receptor-positive breast cancer due to interruption of oestrogen production via the cholesterol-lowering mechanism. Previous epidemiological investigations, however, have found no link between statin use and oestrogen receptor status and the prognosis of breast cancer patients [34]. Body mass index data is also lacking in the used registers. The results of several research have revealed that obese women have a lower prognosis of breast cancer compared with normal-weight women, however other studies with contrary conclusions have also been published. Furthermore, the registries lack data on laboratory investigations, socioeconomic position and factors of lifestyle. Comorbidities are not reported in the FinDM database well enough and were therefore not included in our analysis. The FCR includes some information on cancer treatment delivered, however the data are not complete enough to be included in our analysis. Challenges of confounding by indication are present in observational research, including our study, which covers endpoints that have not previously been studied in randomised controlled trials [35].

An inhibitory action of metformin on breast cancer is biologically possible but the probable mediating mechanism is not understood. Proposed mechanisms include indirect insulin-mediated effects and direct effects on cancer cells via AMPK pathway impact, with subsequent suppression of the mammalian target of rapamycin (mTOR) pathway [36].

CONCLUSION:

Diabetes has been linked to a slightly higher chance of breast cancer diagnosis, an increased risk of recurrence, and an increased risk of developing triple negative tumors. Metformin is an oral hypoglycemic medication that is widely used in the treatment of type 2 diabetes mellitus. It works by increasing fatty acid oxidation, glucose absorption, and nonoxidative metabolism, all of which result in lower blood insulin levels. Metformin causes no hypoglycemia in non-diabetics and has been administered safely in polycystic ovary syndrome and chronic active hepatitis. The leading hypothesis linking metformin's mechanism of action as a chemopreventive agent involves increased activity of the AMPdependent protein kinase (AMPK), a nutrient sensor that inhibits tumorigenesis by targeting tumor metabolism and inhibiting the mTOR-associated oncogenic signaling pathway. In response to growth stimuli, mTOR coordinates dietary availability and energy metabolism. Metformin can inhibit the growth of human malignancies even in the presence of an activating mutation in PIK3CA, another cell metabolic regulator that converges on the mTOR pathway. Many research have been conducted to study the role of metformin in various tumor locations, and some association studies have been published. However, the data is contradictory. Metformin was demonstrated to inhibit breast cancer growth in both ER-positive and ER-negative cell lines in vivo and in vitro, with the impact being higher in ER positive cells.

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