STUDIES REGARDING INTERRELATIONSHIP BETWEEN TYPE 2 DIABETES AND CANCER

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Abstract. Lately, there has been concern about type 2 diabetes occurring in patients previously diagnosed with cancer. To date, the risk of type 2 diabetes patients to develop cancer of different types has been investigated more extensively. This paper has selected data on diabetes in relation with cancer and also with regard to incidence of cancer in relationship to time of diabetes diagnosis. A cohort study to investigate incidence of obesity-related cancers in relation to the time of diabetes diagnosis established that obesity-related and all cancer incidence was increased throughout year two to year five after diabetes diagnosis. In contrast, kidney tumors, pancreas, liver, gallbladder, blood, lung, breast, stomach and thyroid cancers, have been associated with a significantly increased risk of subsequent diabetes, not caused by classical diabetes risk factors. Concomitant viral hepatitis related-cirrhosis and type 2 diabetes increase risk for hepatocellular carcinoma. It was specified that increased mortality in type 2 diabetes patients with cirrhosis and subsequent hepatocellular carcinoma was caused by complications of the liver disease not diabetes' complications. Several limitations of studies associating type 2 diabetes with cancer were underscored, namely that cancer is a plurifactorial process and insulin not a carcinogen respectively, heterogeneity of studies, speculated results and overestimation of study-effects. Advances in molecular biology and methodologies of studies will provide more precise information concerning diabetes as a likely risk factor for developing cancer. On the other hand, diabetes has prognostic value for estimating survival of patients initially diagnosed with cancer and subsequently, type 2 diabetes.
Key words: type 2 diabetes, types of cancer

Rezumat. Una dintre preocupările recente o reprezintă apariţia diabetul tip 2 la pacienţii diagnosticaţi iniţial cu boli maligne. Riscul ca pacienții cu diabet tip 2 să dezvolte diferite tipuri de cancer a fost investigat pe larg. Acest articol a selectat date în ceea ce privește interrelația dintre diabetul tip 2 și riscul de dezvoltare a unor boli maligne, precum și privind pacienți cu boli maligne ulterior diagnosticați cu diabet. Un studiu-cohortă pentru investigarea incidenței cancerelor asociate obezității în corelație cu data diagnosticării diabetului, a stabilit că incidența a fost crescută în intervalul de timp doi-cinci ani de la diagnosticarea diabetului. Prin contrast tumorile de rinichi, pancreas, ficat, colecist, plămân, stomac, tiroidă, cancerul mamar și cancerul limfatic au fost asociate cu riscul crescut de apariție a diabetului după diagnosticarea bolii maligne, în acest caz "diabetul nefiind determinat de factorii tradiționali de risc diabetic". Ciroza apărută în urmă hepatitei virale și concomitentă cu diabetul, crește riscul de carcinom hepatocelular. S-a specificat că mortalitatea în cazul pacienților diabetici cu carcinom hepatocelular, este cauzată de complicațiile bolii de ficat și nu de cele diabetice. Câteva limitări ale studiilor au fost subliniate, respectiv faptul că boala malignă este un proces plurifactorial, insulina nefiind agent carcinogen, heterogenitatea studiilor, rezultatele speculative și supraestimarea efectelor constatate. Progresele din biologia moleculară și cele ale metodologiilor pentru diverse studii vor oferi informații mai precise legate de diabet ca factor de risc pentru dezvoltarea cancerului. Pe de altă parte, diabetul are valoare prognostică pentru estimarea ratei de supraviețuire a pacienților inițial diagnosticați cu boli maligne și ulterior cu diabet tip 2.
Cuvinte cheie: diabet tip 2, boli maligne

INTRODUCTION

Lately, there has been concern about type 2 diabetes occurring in patients with different types of cancer. More data in regard to tumor-induced insulin resistance and diabetes are probably necessary. By now, numerous studies showed that type 2 diabetes patients are at risk to develop cancer. It has been pointed out that the signaling pathways downstream of the activated insulin receptor isoform IR-A and IGF-I receptor are known to stimulate cancer cell proliferation, survival, migration, and invasion, while insulin receptor isoform IR-B is more closely linked to metabolic regulation [1]. Increased IR-A/IR-B ratio and IR-A overexpression determine cancer cells to divide in response to insulin and IGF-II, is produced locally, by both stromal and

epithelial cancer cells. Also, IR-A overexpression in cancer may promote resistance to IGF-I receptor-targeted therapies [2].
This paper has selected data on type 2 diabetes in relation with cancer and also with regard to incidence of cancer in relation to time of diabetes diagnosis.

STUDIES SUPPORTING THE LINK BETWEEN DIABETES AND CANCER

Epidemiological studies that link type 2 diabetes and cancer of different types are complex. Using data of several clinical studies, Matyszewski A. et al. showed C-peptide, insulin and IGFBPs level variations in patients with colon, colorectal and other types of cancers [3]. The authors cited the Physicians' Health Study, a prospective, case control study, which pointed out high C-peptide concentrations in patients with colon cancer. According to this study, subjects of the highest C-peptide concentration quintile were of older ages and had highest levels of risk factors for malignancy like smoking, alcohol consumption, body mass index and lack of physical activity. In patients undergoing surgical treatments for colorectal cancer, the high C- peptide levels were related to increased risk of death. Previously, Djiogue S. et al. have suggested as well that high C-peptide levels associated the risk for colorectal cancer [4]. However, Nogueira L. et al. in 2017 highlighted also in a case control study, which enrolled 1800 subjects that circulating C-peptide concentrations were negatively associated with pancreatic ductal adenocarcinoma only in current smokers. These authors concluded that smoking status is confounding associations between biomarkers of insulin secretion and pancreatic ductal adenocarcinoma [5].
Farrell G. showed in Japanese patients with type 2 diabetes that hepatocellular carcinoma was the most common malignancy, followed by lung, pancreas, and stomach cancer. Diabetes is an independent risk factor for hepatocellular carcinoma HCC that increased risk for the later mentioned by 3- to 4-fold in men, more than 50-fold in obese people with hepatitis B or C, also patients with sustained viral responses and those with hepatocellular carcinoma recurrence after curative therapies [6]. Sharma A. et al. used a score for patients with newly onset diabetes who developed pancreatic cancer - The Rochester Epidemiology Project, 2015. The score (the Enriching New-Onset Diabetes for Pancreatic Cancer ENDPAC) was based on changes in weight, blood glucose and age at diabetes diagnosis. An ENDPAC score of at least 3 identified patients who developed pancreatic cancer three years after diabetes diagnosis ("area under receiver operating characteristic curve 0.87, 80% sensitivity and 80% specificity"). A zero ENDPAC score was found out in patients who had extremely low risk for pancreatic cancer [7].
In an interesting study that investigated the incidence of obesity-related cancers in 71648 women and men, in relationship to the time of diabetes diagnosis, Schrijnders D. et al. established that two to five years after diabetes diagnosis, obesity-related and all cancer incidence was substantially and significantly higher in women and nevertheless, was increased throughout year two to year five after diabetes diagnosis. In men it was suggested that advanced prostate cancer might not be positively related to obesity" as in obese males there were no differences regarding cancer risk after they were diagnosed with diabetes [8]. Also concerning time of diabetes diagnosis and risk of malignancy, de Kort S. et al. noticed an initial spike in colorectal cancer CRC risk in the first six months after type 2 diabetes diagnosis in patients, both men and women, and a subsequent lowering of the effect size of overall CRC risk after these six months were excluded from the statistical analysis [9].
An observational study published last year attempted to show the contrary, namely that diabetes occurred in patients already

diagnosed with cancer [10]. According to this study, nine different types of cancer, namely kidney tumors, pancreas, liver, gallbladder, blood, lung, breast, stomach and thyroid cancers, were associated with a significantly increased risk of subsequent diabetes, which was not caused by traditional diabetes risk factors. Study results reported for more than half a million Korean patients investigated between 2003 and 2013, pointed out that "the risk of diabetes was highest in the two years following cancer diagnosis, and remained elevated during the entire follow-up period. Overall, the hazard ratio (HR) for diabetes associated with cancer was "1.35, after adjusting for sex, metabolic factors, comorbidities and pre-cancer risk factors". The risk for diabetes was increased five-fold in participants diagnosed with pancreatic cancer (HR 5.15), while colorectal and endometrial cancers were not associated with increased risk of subsequent diabetes. Both effects of cancer and treatments of cancer can advance diabetes onset. For example, cachexia as cancer effects is associated with insulin resistance, impaired glucose tolerance, and diabetes [10]. To these studies adds another type of statistical approach, which further concerned survival in cases of patients with hepatocellular carcinoma. Piscaglia F. et al. modeled survival based on clinical parameters, lead-time bias and propensity analysis [11].

A distinct part of researches concerns associations between cirrhosis caused by viral hepatitis, diabetes and hepatocellular carcinoma. In a previous study on hepatitis C virus and diabetes, Hammerstad S.S. et al. showed that there may be no associations between the two pathologies because of subtle variations in HCV genotype, ethnicity and severity of liver disease [12]. In contrast Li J. et al. noted the complex relationships of cirrhosis-related to hepatitis viruses B or C with type 2 diabetes [13]. On one hand, cirrhosis increases risk for type 2 diabetes and on the other hand, existing diabetes accelerates hepatitis C virus infection toward cirrhosis [13]. Furthermore, concomitant viral hepatitis related-cirrhosis and diabetes mellitus increase risk for hepatocellular carcinoma [14]. Ramachandran T.M. et al. specified that increased mortality in diabetic patients with cirrhosis and subsequent hepatocellular carcinoma was not caused by diabetes-related complications but mostly, complications of the liver disease [14]. Concerning antiviral treatments for hepatitis virus C or B, Li J. et al. also underlined that treatments reduced incidence of diabetes mellitus but effects of these treatments on diabetes' complications are by now unknown [13].

STUDIES THAT CONTRADICT THE ASSOCIATION OF DIABETES WITH CANCER

There is also the view that associations of diabetes with cancer are much speculated and both small study-effects and overestimation are found out in investigations addressing this topic.

Godsland I.F. underscored that cancer is a plurifactorial process and considered that "insulin itself does not induce somatic cell mutations and cannot, therefore, be taken into account as carcinogen". "Pre-malignant lesions may be present in a high proportion of healthy individuals, and these lesions might progress to invasive cancer" only through imbalances, metabolic abnormalities and inborn errors of metabolism [15]. Also, according to Godsland I.F. diabetic patients could be at the same time relatively hypoinsulinemic and consequently considered, at low risk of developing cancer. Another specification Godsland I.F. made, concerns very difficult recruitment of study-patients. Participants enrolled in a study are supposed to undergo numerous investigations during a long period of time. Tsilidis K.K. et al. reported in a meta-analysis, substantial heterogeneity between studies, small study effects and excess

significance, all three because of which, associations between type 2 diabetes and risk of hepatocellular and pancreatic cancers may be invalidated [16].
Additionally, there was reservation about researches, as for example, in case- control studies IGF-1 can reflect tumor metabolism also, and therefore should not be taken into account as impact on risk of developing cancer [17].

CONCLUSION

Advances in molecular biology and methodologies of studies will help provide more precise information for taking into account, on one hand insulin resistance and diabetes as likely risk factors for developing cancer. On the other hand, diabetes has prognostic value for estimating survival of patients with cancer.

Conflicts of interest

The authors declare no conflicts of interest.

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