# Editorial

## Metformin Prevents Cancer in Type 2 Diabetes

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Diabetes and cancer represent two chronic, severe, heterogenous conditions, presenting a multifactorial etiology. Epidemiological studies clearly indicate that the risk for several types of cancer (pancreas, liver, breast, colorectal, genital, urinary tract) is increased in patients suffering from diabetes. Mortality is also moderately increased. A lot of factors may influence the risk for developing cancer: diabetes duration, degree of metabolic control, antidiabetic medication, presence of chronic complications. Hyperinsulinemia is quite likely to favour cancer in patients with diabetes, because it represents a growth factor with metabolic and also mitogenic effects. On the cancerous cell, insulin acts both at the receptor level and also after the receptor. Obesity, hyperglicemia and increase of oxidative stress may also contribute to the increase of cancer risk in diabetes. Anticancer drogs may increase the diabetes risk or may aggravate it [14]. There is more and more brought into discussion the role of the antidiabetic treatment and cancer appearance or progression. Although the association between type 2 diabetes mellitus and various cancer types in humans is well-established, few studies have investigated the role of antidiabetic therapies in this relationship [1].

During the 45th EASD (European Association for the Study of Diabetes) Congress on October 1st 2009, in Vienna, Becky McCall presented the results of an epidemiological, observational study which placed Metformin as a protector against pancreas and colon cancer, in patients suffering from type 2 diabetes [18]. This study took place over a period of 5 years, on a group of patients treated with insulin and another group of patients treated with metformin. The patients treated with insulin developed colon cancer twice more frequently than patients treated with metformin and four-five more times pancreas cancer [18]. The study was retrospecive and brought in information about the treatment of patients with diabetes from 300 GPs. There were excluded the patients previously known as having cancer and there were included only the patients who started the treatment after 2000. Insulin exposure was estimated after the number of annual prescriptions (classified as <7, 7–10, 11–15, or >15). The researchers analysed the data from 4829 patients treated with insulin (11415 patient-years), 5035 treated with insulin plus metformin (15725 patient-years), and 30421 treated only with metformin (71261 patient-years). The main objective was the diagnosing of solid tumor for the first time. The global rate of cancer was of 60 events in 1000 patient-years in the group treated only with insulin, in highest dose, comparatively to 34 cancer events in 1000 patient year in the group treated with insulin plus metformin [18].

After the age, sex, smoker/ non-smoker status adjustment, the same ratio was true for insulin plus metformin vs. insulin only (5.73 vs 3.20) [18].

Craig Currie, PhD, a medical epidemiologist within the Cardiff University in Wales, who was the study co-author, said: "In the insulin-only group, there was a distinct relationship correlated with age, with a six times increase in all cancer forms in the group with highest doses, comparatively with the patients who underwent metformin mono-therapy. This dose-answer relationship suggests a causal one, but various studies are required in this sense. The metformin seems to have a protective role, but this issue also requires future studies [18].

As Chairman of the Session, the current president of EASD, Ulf Smith, MD, from Sahlgrenska University Hospital in Göteborg, Sweden, stated that there are necessary many more studies in order to declare whether there really exists a relationship between increased doses of insulin and cancer or whether the cause may be insulin resistance, associated with type 2 diabetes. There are reasons to involve insulin resistance per se [18].

Pancreas cancer represents the fourth cancer cause of death, in the USA, both in women and in men [2]. Although type 2 diabetes may appear as a consequence of pancreas cancer, there have accumulated proofs that support the influence of antidiabetic treatment in pancreatic carcinogenesis [2]. Metformin seems to reduce the risk of pancreas cancer, while insulin and sulphonylureas seem to increase it [1], according to the results of a greater case-control study, published in August 2009 in "Gastroenterology".

Donghui Li et all published in 2009, in "Gastroenterology" Journal, Vol. 137, No.2: 482 -488, the article „Antidiabetic Therapies Affect Risk of Pancreatic Cancer". They published the results of a case-control study developed within M.D. Anderson Cancer Center, Houston, Texas, from 2004 until 2008. 973 patients with pancreatic adenocarcinoma were introduced in the study. (out of which 259 suffered from diabetes, 59,7% men) and 863 control subjects (out of which 109 suffered from diabetes, 63,2% men). The conclusions of the study were the following: metformin was associated with a low risk and insulin or insulin secreting drods were associated with an increased risk of pancreas cancer in patients with diabetes. This case-control study is the first one that shows a statistically significant association between antidiabetic therapy and the risk of pancreas cancer. The most important result is that patients with diabetes who were never treated with metformin, especially on a period of time longer than 5 years, presented a higher risk than the ones who were treated with metformin (odds ratio, 0.38; 95% confidence interval, 0.22-0.69; $P = 0.001$). After the exclusion from the study of patients with a time period $\leq 2$ year (considering that a pancreas cancer that may have led to a secondary diabetes would have rapidly evolved), the protective effect of metformin against pancreas cancer remained a statistically significant one. In contrast, the patients who were treated with insulin or insulin secreting drogs (sulpholynureas and meglitinides) presented a higher cancer risk than those who never received insulin. These observations are in accordance with the results

from two other previous epidemiological studies [3,4].

An increasing risk for pancreas cancer was also established in patients treated with thiazolidinediones, a drog that increases the insulin sensibility (an action similar to metformin), comparatively to those who never received this treatment, but insignificant from a statistic point of view ($P = 0.213$), and from this comes the unsustainable idea that the anticancer action of the metformin may be due to the insulin resistance improvement [1].

Other factors associated with diabetes, such as: diabetes duration, smoking, overweight and obesity, glycemic control, did not have a significant influence on the relationship between metformin and the risk for cancer [2].

Metformin reduces glycemia by decrease of hepatic glucose production, by increase of glucose use and by oxidation of fatty acids. Metformin reduces the level of plasmatic insulinemia [5]. Metformin hardly reduces the body weight, while other therapeutical classes increase it [6]. The direct action mechanisms of metformin involve the activation of adenosine mono-phosphate protein kinase that belongs to the protein-kinase family sensitive to metabolites, and sensitive to the increase of adenosine monophosphate [7]. Adenosine monophosphate activated protein kinase plays not only the role of activating a lot of enzymes that interfere with the metabolism, but it was shown that they might even inhibit the mTOR pathway, which may balance the cellular proliferation [8]. Moreover, the adenosine monophosphate activated protein kinase has been quite recently involved in cell polarity and cell division [9]. Thus, besides hyperglycemia and hyperinsulinemia improvement (factors that mediate the adverse effect of diabetes on cancer), metformin has got direct effects on cancer cells, thus blocking mitogenic effects of insulin and of insulin-like growth factor I after the receptor, by blocking the phosphatidylinositol 3-kinase/Akt/mTOR signaling pathway and by inhibiting cell division. The experiments on cell cultures as well as on animal pattern have shown direct anti-cancer effects of metformin [10,11, 12].

A study regarding prostate cancer [13] was performed in Finland, on 24,723 case-control pairs. The risk for prostate cancer was lower in patients who received any kind of antidiabetic drog. Due to the low number of patients on rosiglitazone and insulin, their effect could not be analyzed. [13].

Another group of researchers [15] studied the association between the hepatocellular carcinoma and type 2 diabetes, involving in the study 465 patients with hepatocarcinoma, 618 with cirrhosis and 490 control subjects. They showed that type 2 diabetes represents an independent risk factor for hepatocarcinoma and it previously exists in the majority of patients. Moreover, in men with type 2 diabetes there was established a direct association between the hepatocarcinoma with an insulin treatment and the one with sulphonylurea treatment and a reverse relationship with metformin [15].

Various authors [16] from the Department of Breast Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, 77030-4009, USA wanted to determine whether the use of metformin may be associated with the favourable therapeutic answer to the chemotherapy treatment. There was established that the patients with diabetes

and cancer who were treated with metformin had a better answer to the chemotherapy treatment than the patients with diabetes who were not treated with metformin [16]. Nevertheless, there are still necessary additional studies that may guarantee the antitumor potential of metformin.

Nick Mulcahy [17] comments on the results of several studies that showed an association between the C-peptide concentration, BMI (Body Mass Index) and the unfavourable evolution of prostate, colorectal and endometrial cancer, simultaneously with their increase. It is suggested the positive role that metformin may play in decreasing insulinemia. All these data require prospective studies, with clear protocols, that will have as main objective the effect of antidiabetic therapy on the risk for cancer or the role of metformin as a therapeutic response to cytostatics in patients with or without diabetes mellitus.

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