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EDITORIAL

Metformin and cancer: Technical and clinical implications for FDG-PET imaging

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Abstract

Metformin is the most widely used hypoglycemic agent. Besides its conventional indications, increasing evidence demonstrate a potential efficacy of this biguanide as an anticancer drug. Possible mechanisms of actions seem to be independent from its hypoglycemic effect and seem to involve the interference with key pathways in cellular proliferation and glycolysis. To date, many clinical trials implying the use of metformin in cancer treatment are on-going. The increasing use of ^{18}F-2-fluoro-2-deoxy-d-glucose positron emission tomography (FDG-PET) in cancer evaluation raises a number of questions about the possible interference of the biguanide on FDG distribution. In particular, the interferences exerted by metformin on AMP-activated protein kinase pathway (the cellular energy sensor), on insulin levels and on Hexokinase could potentially have repercussion on glucose handling and thus on FDG distribution. A better comprehension of the impact of metformin on FDG uptake is needed in order to optimize the use of PET in this setting. This evaluation would be useful to ameliorate scans interpretation in diabetic patients under chronic metformin treatment and to critically interpret images in the context of clinical trials. Furthermore, collecting prospective data in this setting would help to verify whether FDG-PET could be a valid tool to appreciate the anticancer effect of this new therapeutic approach.

Key words: Metformin; Cancer; ^{18}F-2-fluoro-2-deoxy-d-glucose positron emission tomography; Diabetes; Glucose metabolism

Core tip: Given the recent increasing number of clinical trials involving the use of metformin as anticancer agent and with the widespread use of ^{18}F-2-fluoro-2-deoxy-d-glucose positron emission tomography (FDG-PET), this editorial deals with a critical evaluation of the main variables regulating FDG uptake that could be potentially influenced by the biguanide. This analysis could optimize not only the interpretation of PET images in diabetic patients but could also help to verify whether FDG-PET could be a valid tool to appreciate anticancer potential of this new therapeutic approach thus opening a new window on clinical trials.

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INTRODUCTION

Due to its safety, tolerability, and a very low incidence of lactic acidosis[1], metformin is the most widely prescribed oral hypoglycemic agent and exerts this effect by reducing hepatic glucose production and by increasing insulin sensitivity as well as glucose use by peripheral tissues[2,3]. Besides diabetes and other established indications for metformin[4,5], increasing evidence demonstrate a possible efficacy of this agent as an anticancer drug[6].

METFORMIN AND CANCER

The hypothesized beneficial actions of metformin against cancer involve different and not yet fully clarified mechanisms. A key role is believed to be mediated by AMP-activated protein kinase (AMPK), a major player in the regulation of metabolism and growth, for both normal and cancer cells[7]. The activation of this molecule results from a decrease in mitochondrial ATP production due to the direct inhibition of metformin on respiratory complex Ⅰ[8] and consequently of the mammalian target of rapamycin. This effect induces cell cycle arrest and inhibits protein synthesis in cancer cells. However, more recent data have suggested that metformin can also regulate cancer cell biology in an AMPK-independent manner through the inhibition of the unfolded protein response with a consequent apoptosis, preventing angiogenesis and exerting toxicity on cancer stem cells[9].

Several recent epidemiological, animal, and cellular studies support these findings and a recent meta-analysis has highlighted a correlation between decreased incidence of cancer and treatment with metformin in type Ⅱ diabetes patients[10-12].

Taken together these findings have encouraged more than 100 clinical trials on the effect of this drug in cancer patients, including prevention, adjuvant treatment and palliative treatment (cfr. on the NIH ClinicalTrials.gov web site[13]).

METFORMIN AND FDG-PET IMAGING: TECHNICAL AND CLINICAL IMPLICATIONS

The increasing widespread use of ^{18}F-2-fluoro-2-deoxy-d-glucose positron emission tomography (FDG-PET) for the imaging of neoplastic disease[14] raises a number of questions about the possible technical and clinical implication of metformin on this technique.

In particular, can metformin interfere with FDG distribution in the whole body or in cancer tissue? And, if so, how should we interpret FDG PET scans in diabetic patients under chronic treatment with the biguanide? Finally, can this tracer be used to test and assess the antineoplastic effect of metformin on cancer?

In clinical practice, the use of FDG-PET to non-invasively diagnose, monitor, and evaluate treatment response of cancers is well established from many years[15]. This concept was extended from the observation by Di Chiro *et al*[16] who firstly demonstrated that FDG was more avidly accumulated in human brain tumors than in surrounding brain as well as in tumor recurrence.

The evaluation of gastro-intestinal tract is a well-known pitfall in FDG-PET imaging interpretation. Actually, metformin leads to intense, diffusely increased intestinal FDG in the colon, and to a lesser extent in the small bowel[17]. This effect can limit the diagnostic capabilities of FDG-PET/CT scanning and may mask gastrointestinal malignancies potentially resulting in incorrect cancer staging, inability to detect second primary cancers and inability to assess response to therapy[18,19]. To solve this problem, some authors proposed drug discontinuation before imaging with different schemes[20,21], in order to improve image analysis. However, to date there is no agreement about which is the best approach and feasibility and washout duration still have to be verified in the clinical setting.

Our group[22] has tried to elucidate the determinants of high intestinal ^{18}F-FDG radioactivity content in a mouse model, treated with long- or short-term metformin administration. We showed that this phenomenon, appearing after a relatively long period of treatment and persisting soon after drug washout, was related to biguanide-induced modifications in the gut cell phenotype and was characterized by an ATP-depletion with the consequent increased phosphorylated-AMPK levels and reduced *TXNIP* gene expression.

With these premises, it is evident that the consequences of metformin treatment on FDG-PET scans are difficult to predict. On one side, as a drug with anti-proliferative activity metformin should decrease FDG uptake; on the other side, by activating AMPK in tumors, it would be expected to increase their glucose metabolism.

A further factor that has to be taken into account when we use FDG in cancer evaluation during metformin treatment is insulin asset[23]. As mentioned before, some recent experimental models have reported that one of the possible mechanism by which metformin could exert an antineoplastic activity, is its capability to lower both glucose and insulin levels in type II diabetes patients[24,25]. In order to examine this aspect, Mashhedi *et al*[26] studied FDG distribution in an example of insulin-responsive tumor. In a murine colon

cancer model, they found that metformin exposure did not affect insulin levels nor tumor FDG uptake in normo-insulinemic mice while decreased insulin levels and FDG uptake in hyper-insulinemic mice suggesting that, at least in this model, in neoplastic tissue the effect of this compound on insulin levels was more important than any AMPK activation.

This observation would imply carefulness in the evaluation of clinical trials using metformin in cancer treatment because its effect could be limited to hyper-insulinemic subjects with insulin sensitive neoplasms. As a consequence, it has also important implications on for the interpretation of FDG-PET images and on for understanding influences of exerted by host metabolism and metformin on tumor behavior.

Another important role of metformin that could be involved in antineoplastic activity and thus can interfere with FDG uptake, is its capability to directly and selectively inhibit the enzymatic function of hexokinase (HK) Ⅰ and Ⅱ as demonstrated by Marini *et al*[27]. This work extended previous evidence about metformin *in vitro* effect in different cancer models such as CALU-1 cells as a model of non-small cell lung cancer[28] and in MDA-MB231 as a model of triple negative breast cancer. In all these cells metformin determined a dose- and time-dependent reduction in FDG uptake, in agreement with the expected effect of the biguanide on AMPK phosphorylation. Interestingly, this molecular mechanisms rely on the dislocation of HK from outer mitochondrial membrane with a consequent loss of enzymatic functional properties.

By interfering with HK activity, a rate limiting step of glucose consumption, metformin could influence FDG uptake. In fact, even if unquestionable evidence attesting that it is the exact surrogate and has the same metabolic fate of glucose is still lacking, we know that this tracer enters within the cell through the same facilitative transporters of glucose, is then phosphorylated by HK to FDG6P and remains trapped within cytosol, preventing all further glycolytic reactions.

Obviously, all these findings cannot be easily transferred in clinical practice due to the high doses needed to induce this response (750 mg/kg per day) in mice. However, they rise up some interesting reflections. Metformin could influence some important determinants of FDG uptake in the different tissue: by lowering serum glucose and insulin levels it could modify tracer availability in the blood, reducing the usual competition between glucose and FDG for GLUT-1 receptor and other glucose transport proteins. This could lead to an increase in tracer availability for lesion uptake making the simple measurement of lesion tracer uptake (the so called SUV) a suboptimal index of lesion metabolism.

Even more complex is to establish whether FDG-PET could represent a correct technique in for the assessment of the potential antineoplastic effect of metformin in the clinical setting.

In this line, it is of primary importance to understand how metformin could modulate PET signal in order to correctly verify whether this technique is useful to asses any therapeutic response.

This task is particularly relevant when metformin is used as adjuvant with other conventional therapy such as chemotherapeutic agents able to alter FDG distribution *per se*.

In apparent disagreement with other evidence[27], Habibollahi *et al*[29] showed that, in two colon cancer models, metformin increased ^{18}F-FDG uptake soon after initiation of treatment. However, as the cells die from the effects of the biguanide and other chemotherapies, ^{18}F-FDG uptake should eventually decrease. But this possible biphasic response on ^{18}F-FDG PET scans could confound the evaluation of therapeutic efficacy leading to an incorrect classification of patients as non-responders on the basis of an earlier scan.

To date, present available clinical trial results on the use of metformin as anticancer agent involve intermediate or surrogate outcome measurements, such as changes in cellular proliferation or hormone levels, rather than direct measures of clinical benefit and thus do not allow definitive conclusions. Furthermore, with respect to the colon, available data deal with the effects of metformin, at least in non-diabetic subjects, on normal epithelial cells rather than cancer cells and thus hypotheses concerning the use of this drug for prevention rather than for treatment are more feasible[30].

FUTURE DIRECTIONS

Prospective trials in diabetic patients submitted to routine FDG-PET scans are mandatory to verify if FDG-PET can be used as an early marker of response or if metformin interference with FDG distribution is significant enough to prevent its use in this setting and, in this case, if the use of proliferation markers would be preferable as appropriate choice to image the response of tumors.

To this purpose, a possible approach could be the use of compartmental analysis of tracer through dynamic PET acquisition in order to measure cancer glucose consumption in absolute terms (micromole/min/g) and to obtain information about the possible relationship with lesion progression and therapeutic response.

CONCLUSION

FDG PET is useful to evaluate cancer metabolism in response to the different interventions. In order to establish if this technique could be a valid tool to appreciate anticancer potential of new therapeutic approach such as metformin, a better comprehension of all the variables that could interfere with FDG uptake is needed and further studies in this field are required.

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