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Cancer, obesity, and diabetes: TKIs exert multiple effects on glucose homeostasis

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Cancer, obesity, and type II diabetes mellitus (T2DM) are becoming increasingly prevalent worldwide; a greater understanding of the links between these medical conditions is urgently needed in order to identify novel targets for treatment. In a Review published in the February 2017 issue of this distinguished journal (Cancer, obesity, diabetes, and antidiabetic drugs: is the fog clearing? *Nat. Rev. Clin. Oncol.* **14**, 82–99; 2017)[1], Klil-Drori *et al.* summarize the current evidence regarding the relationships between obesity, T2DM, and cancer. We completely agree with the authors' statements regarding the influence of various medications used to treat diabetes on cancer development and/or outcomes. Moreover, we appreciate the clear evidence presented by the authors that, conversely, some anticancer treatments can perturb glucose homeostasis and, therefore, lead to or exacerbate hyperglycaemia and T2DM. This Review neglects, however, the potential effects of tyrosine-kinase inhibitors (TKIs) that are used routinely in the treatment of cancer on glycaemic control.

TKIs are now used successfully in the treatment of many malignancies. Many of these agents target signalling pathways that influence cellular glucose metabolism, and increasing amounts of data demonstrate that TKI therapy can result in either elevated or decreased blood glucose levels, depending on the agent used and the clinical context[2,3] (TABLE 1). In some settings, hyperglycaemia has been reported as a common adverse effect of TKI therapy[4]. Generally, however, TKIs contribute to lower glucose level and, thus, improve glycaemic control. In one study[5], the hypoglycaemic effects of imatinib, dasatinib, sorafenib, and sunitinib occurred in both diabetic and nondiabetic patients, but the exact underlying mechanisms remain to be determined. Importantly, this effect might actually be beneficial for patients with T2DM by enabling them to discontinue antidiabetic drugs; in the aforementioned study[5], eight of the 17 diabetic patients (47%) attained a level of glycaemic control with TKI therapy that enabled them to discontinue their antidiabetic medications, including insulin in some patients.

Of note, some TKIs (for instance, imatinib and sunitinib) have been associated with both hyperglycaemia and hypoglycaemia[6,7], adding an additional layer of complexity. Indeed, certain TKIs can exert totally opposite glycaemic effects in different types of cancer. In a case report involving a patient with a relapsed and refractory abdominal solitary fibrous tumour, sorafenib treatment — given in the context of an initial misdiagnosis of refractory gastrointestinal stromal tumour — was effective in controlling persistent non-islet-cell tumour-induced hypoglycaemia (NICTH)[8]. NICTH is caused by overexpression of insulin-like growth factor II (IGF-II) by tumour cells; therefore, the observed effect of sorafenib on hypoglycaemia was probably due, in part, to tumour-cell killing — as supported by evidence of intratumoural necrosis on CT scans[8]. Nevertheless, the glycaemic control might also have been partially attributable to inhibition by sorafenib of receptor-tyrosine kinases that mediate glucose metabolism. By contrast, in addition to the hypoglycaemic effects of sorafenib when used in approved indications[5], this agent has also been associated with triggering of recurrent nonhyperinsulinaemic hypoglycaemia (in a wax and wane pattern) in a patient with haemangiopericytoma who had never previously experienced hypoglycaemia[9]. The mechanisms contributing to hypoglycaemia in this case might also have been associated with NICTH because the patient's serum IGF-II levels were slightly elevated; however, the possibility that hypoglycaemia resulted from the activity of sorafenib itself and/or the effects of this agent on tumour burden cannot be excluded[9].

In summary, TKIs exert markedly different effects on glucose homeostasis according to the particular TKI or the type of tumour involved. Thus, research investigating the relationships between these anticancer agents, diabetes, and cancer is urgently needed.

Table 1 | **Effect of TKIs approved for the treatment of cancer on glucose homeostasis**

TKI	Approved indications	Effect on glucose levels
Imatinib	CML, CEL, ALL, and GIST	• Hyperglycaemic effect[7] • Hypoglycaemic effect[10]
Nilotinib	CML	Hyperglycaemic effect[4]
Dasatinib	CML and ALL	Hypoglycaemic effect[11]
Gefitinib	NSCLC	Hyperglycaemic effect[12]
Erlotinib	NSCLC, gastic cancer, and PDAC	Hypoglycaemic effect[13]
Sorafenib	RCC and HCC	Hypoglycaemic effect[5]
Sunitinib	RCC, GIST, and PNET	• Hyperglycaemic effect[14] • Hypoglycaemic effect[15]

ALL, acute lymphoblastic leukaemia; CEL, chronic eosinophilic leukaemia; CML, chronic myeloid leukaemia; GIST, gastrointestinal stromal tumour; HCC, hepatocellular carcinoma; NSCLC, non-small-cell lung carcinoma; PDAC, pancreatic ductal adenocarcinoma; PNET, pancreatic neuroendocrine tumour; RCC, renal-cell carcinoma.

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Competing interests statement
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