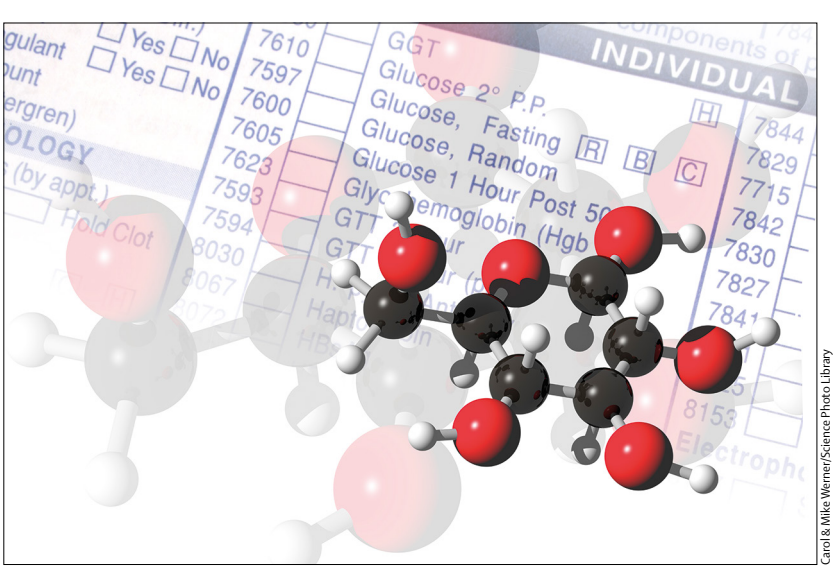
Quackery
Insulin potentiation therapy for cancer?

Insulin is responsible for cellular glucose uptake and mitogenic signalling cascades in cancer cells,[1] and can promote cell proliferation, survival, invasiveness, angiogenesis, immunomodulation, and chemoresistance.[1–3] Why, then, would some medical practitioners claim that the use of insulin and glucose can improve the outcomes of patients with cancer and facilitate cancer therapy de-escalation?[4,5]

In 1930, Donato Perez Garcia (Mexico City, Mexico) hypothesised that insulin increases cell permeability to certain therapeutics.[5] Modern supporters of insulin potentiation therapy (IPT) and IPT with low-dose chemotherapy (IPTLD) for patients with cancer claim that insulin increases cancer cells' permeability to chemotherapeutics relative to surrounding healthy tissues, because of the high expression of insulin receptors on these cells.[4] They suggest several mechanisms to explain this hypothesis: alterations of cellular lipid synthesis that change the lipid constituents of the cell membrane, drug adsorption onto glucose molecules, and adsorption of drug molecules onto insulin followed by receptor-mediated endocytosis.[4,6] Other supporters suggest anticancer drugs enter cells through the same mechanism as that of glucose, conflating glucose transport with multidrug uptake transport. According to IPT supporters, cancer cell selectivity of insulin-induced permeabilisation is conducive to lowering the dose of anticancer drugs, thereby mitigating toxicity while retaining therapeutic benefit. Thus, they recommend doses of anticancer drugs that are reduced upward of 75–90% from the approved standard of care, without any definitive clinical data to support similar benefit from this de-escalation strategy.[4]

The mechanistic explanation for IPT is pseudo-scientific. Research has consistently shown that drug disposition is a function of the physiochemical properties of individual molecules (size, lipophilicity, and charge), various physiological factors (eg, plasma binding proteins, ion gradients, blood flow), and carrier proteins (ie, drug transporters).[7] Insulin-mediated membrane cellular permeability to glucose is itself a function of the expression of GLUT transporters,[8] and it is well established that glucose is not lipophilic enough to simply diffuse through the plasma membrane.[9,10] Methotrexate, a drug that can be used as a chemotherapeutic, is even less lipophilic than glucose and does not cross lipid-containing plasma membranes at biological concentrations,[9] yet IPT supporters claim that methotrexate enters cells because of the increased membrane permeability achieved with IPT.[4,11] Regardless of their lipophilicity, most small-molecule oncolytic drugs are also substrates for transporters that move therapeutics in an extracellular to intracellular direction (uptake) or vice versa (efflux).[12] No evidence shows any insulin-regulated glucose transporter simultaneously transporting drug molecules.[13] We searched PubMed on Nov 30, 2018, and found no studies of receptor-mediated endocytosis of a drug molecule bound to endogenous glucose or endogenous insulin, despite some claims to the contrary.[6]

Insulin does increase methotrexate uptake in vitro in a breast cancer cell line (MCF-7) while simultaneously increasing its cytotoxicity,[14] which is consistent with the claims of IPT supporters.[4] However, insulin treatment only increases cellular uptake of methotrexate to a minor extent over a short period of time, and insulin-treated cells have the same steady-state methotrexate uptake as untreated cells. Differences in cellular uptake do not explain an approximate 10 000-times increase in methotrexate cytotoxicity in MCF-7 cells exposed to insulin.[14] The increase in both intracellular methotrexate concentration and cytotoxicity after insulin exposure is attributed to augmentation of methotrexate poly-glutamate synthesis,[15,16] and downregulation of a methotrexate efflux transporter (ABCB1) in MCF-7 cells.[17,18] Thus, insulin can affect certain cellular pathways that alter methotrexate exchange in this particular breast cancer cell line, but does not increase membrane permeability to methotrexate or facilitate its transport bound to either glucose or insulin. A systematic review of preclinical studies showed that, of 23 cancer cell lines of



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For a full reference list see **Online** for appendix

For more on the **claims on IPT** see https://euromedfoundation.com, http://donatoperezgarcia.com, and http://contemporarymedicine.net/insulin-potentiation-therapy/

For more on **IPT therapy cost** see https://www.arizonaadvancedmedicine.com/Articles/2018/June/Frequently-Asked-Questions-About-IPT-LD.aspx

For more on **crowdfunding for IPT** see https://www.kotsanisinstitute.com/services/cancer-treatment

For more on the **Academy for IPT** see http://iptldacademy.org/

multiple histologies, only five (22%) showed increased chemotoxicity when treated with anticancer drugs in a high-glucose environment.[19]

There are only two published clinical trials assessing IPT.[20,21] A study including 16 patients with castration-resistant prostate cancer tested insulin (0·4 U/kg) and goserelin depot (3·6 mg/m²) with either docetaxel (3·6 mg/m²) or a non-standard drug combination for this setting: insulin (0·4 U/kg) with cyclophosphamide (0·10–0·15 g/m²), epirubicin (3 mg/m²), and vinblastine (0·5 mg/m²) in unconventional cycles.[20] All patients also received dexamethasone (20 mg), cyclophosphamide (50 mg), doxycycline (100 mg), celecoxib (15 mg), legalon (a milk thistle formulation), antioxidants, and ozone therapy. The standard dose of docetaxel in this population is 75 mg/m² once every 3 weeks. The study appears to have been done in an integrative medical centre and the publication does not mention ethics approval. Though the study claims no significant side-effects were observed, it also reports five (31%) of 16 patients required blood transfusions, an intervention indicative of grade 3 or higher anaemia as per Common Terminology Criteria for Adverse Events, version 5. Oddly, seven (44%) of 16 patients discontinued treatment for financial reasons—the therapy was not covered by insurance. After ten cycles of IPT, an overall response was achieved in four (44%) of nine patients who received treatment; however, responses were not recorded in accordance with the Prostate Cancer Working Group 2 guidelines.[22] Median overall survival was 11 months (95% CI not reported) with this therapy compared with 18·9 months (95% CI 17·0–21·2) with standard docetaxel.[23] Yet, IPT providers frequently cite this study to justify their use of IPT. The second prospective study examined methotrexate response and toxicity in 30 patients with metastatic breast cancer who previously had standard hormonal therapy or chemotherapy. Patients received one of three treatments (n=10 each): insulin (0·3 U/kg) plus methotrexate (2·5 mg/m²), methotrexate alone (2·5 mg/m²), or insulin alone (0·3 U/kg), all administered in a 30% glucose solution. Stable disease was reported to be more frequent in the group receiving methotrexate plus insulin than those receiving methotrexate alone (90% *vs* 30%, respectively).[21] An increase in the proportion of patients who achieved stable disease in this small study is hardly sufficient to suggest that IPT plus methotrexate is in any way an improvement over approved therapies used for breast cancer.

We searched ClinicalTrials.gov on Nov 30, 2018, with the terms "insulin potentiation" and "cancer", and found two registered trials. One was withdrawn (NCT02598479) while results for the second trial are 4 years overdue (NCT01539148). Further clinical evidence on IPT is not likely to be forthcoming and stands in stark contrast with the claims of supporters who say IPT is safe and effective.[4]

On the contrary, there is substantial scientific evidence that insulin treatment and increased concentrations of intracellular sugars accelerate both tumour progression and chemoresistance. Since the 1920s, peer-reviewed literature has shown that cancer cells consume glucose at a rate above that required for ATP synthesis, and ferment glucose into lactate to maintain aberrantly high proliferation.[24] Many tumours express GLUT transporters and become insulin-sensitive.[25] Activation of insulin and insulin-like growth factor (IGF) signalling has been associated with the development and progression of different cancers, prompting extensive, ongoing research to improve current cancer prevention interventions and investigate drugs targeting this pathway.[26] The proposed antitumour effect of metformin, a drug that lowers blood glucose concentrations, has been attributed to activation of the liver kinase B1/AMP-activated protein kinase/mammalian target of rapamycin pathway and the direct inhibition of the insulin/IGF pathway.[27,28] Despite numerous clinical trials investigating metformin, no phase 3 trial has shown the clinical benefit of such treatments for patients with cancer. Poorly regulated glucose metabolism, however, has been associated with disease progression and drug resistance in cancer patients.[29] These results are concerning since the IPT protocol[11] includes administering insulin to fasting patients followed by reduced-dose chemotherapy and 10–25 g of intravenous glucose.[25,27,28]

The economic burden and medical ethics of IPT are also concerning. Although most IPT providers do not post their prices, one integrative medical centre in the USA, the Arizona Center for Advanced Medicine, quotes US$50 000 for the first 2 months of IPT treatment, associated evaluations, lab tests, and group discussions. This price does not include the costs of chemotherapy and other drugs. Another website offers financing options and help with organising crowdfunding campaigns, since insurance is not likely to cover the treatment. The cost for IPT is an out-of-pocket expense for patients that probably exceeds the cost of the same chemotherapy provided as standard of care.[30] Of further concern, the Academy for IPT publishes a list of approximately 65 IPT practitioners worldwide, with two practitioner associations in Germany and Russia whom this organisation certifies. Desperate patients often turn to unproven therapies; unfortunately, only IPT practitioners stand to benefit.

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