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Sulfonylurea derivatives and cancer, friend or foe?

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Gliclazide (PubChem ID: 3475)
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ABSTRACT

Type 2 diabetes mellitus (T2DM) is associated with a higher risk of cancer and cancer-related mortality. Increased blood glucose and insulin levels in T2DM patients may be, at least in part, responsible for this effect. Indeed, lowering glucose and/or insulin levels pharmacologically appears to reduce cancer risk and progression, as has been demonstrated for the biguanide metformin in observational studies. Studies investigating the influence of sulfonylurea derivatives (SUs) on cancer risk have provided conflicting results, partly due to comparisons with metformin. Furthermore, little attention has been paid to within-class differences in systemic and off-target effects of the SUs. The aim of this systematic review is to discuss the available preclinical and clinical evidence on how the different SUs influence cancer development and risk. Databases including PubMed, Cochrane, Database of Abstracts on Reviews and Effectiveness, and trial registries were systematically searched for available clinical and preclinical evidence on within-class differences of SUs and cancer risk. The overall preclinical and clinical evidence suggest that the influence of SUs on cancer risk in T2DM patients differs between the various SUs. Potential mechanisms include differing affinities for the sulfonylurea receptors and thus differential systemic insulin exposure and off-target anti-cancer effects mediated for example through potassium transporters and drug export pumps. Preclinical evidence supports potential anti-cancer effects of SUs, which are of interest for further studies and potentially repurposing of SUs. At this time, the evidence on differences in cancer risk between SUs is not strong enough to guide clinical decision making.

1. Introduction

Patients diagnosed with type 2 diabetes mellitus (T2DM) have an increased risk of cancer and cancer-related mortality (Chen et al., 2017b; Giovannucci et al., 2010). This increased risk is already present before diagnosis of T2DM (de Kort et al., 2017; Redaniel et al., 2012; Schrijnders et al., 2018; Yu et al., 2016). T2DM is characterized by insulin resistance, hyperglycemia and hyperinsulinemia, which have all been associated with cancer development (Jalving et al., 2010; Yang et al., 2010a. Cancer cells have an altered energy metabolism characterized by high glucose consumption and high glycolysis rates. This provides energy to generate ATP as well as metabolic intermediates for production of biomass required for cellular proliferation (Liberti and Locasale, 2016). This so-called metabolic reprogramming is one of the hallmarks of cancer (Hanahan and Weinberg, 2011). The metabolic characteristics of tumors and their microenvironment are increasingly important for understanding cancer development, treatment resistance and for the identification of novel treatment targets (Pavlova and Thompson, 2016). Therefore, investigation of factors associated with cancer development in T2DM patients is of particular interest.

Increased plasma glucose and insulin levels are, at least in part, responsible for the increased risk of cancer and cancer related mortality of T2DM patients (Ariaans et al., 2015). The various classes of glucose-lowering agents have different mechanisms of action, and thus differential effects on plasma glucose and insulin levels and different off-target effects. Therefore, these classes of drugs may also differ in their influence on cancer risk and development. Preclinical studies in cancer models and observational clinical evidence indicate anti-cancer effects of the biguanide metformin and clinical trials testing effectivity of metformin in cancer patients are ongoing (Jalving et al., 2010; Soranna

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et al., 2012). For the other important class of oral glucose lowering drugs, the sulfonylurea derivatives (SUs), available data is conflicting (Chen et al., 2017a; Currie et al., 2013; Hsieh et al., 2012; Mamtani et al., 2014; Morgan et al., 2012; Qiu et al., 2013). Several studies have reported an association between increased cancer risk and use of SUs in T2DM patients, in some cases potentially confounded by the use of metformin as a comparator (Chen et al., 2017a; Thakkar et al., 2013; Yang et al., 2010a). Other studies have shown that SU use did not increase cancer risk in T2DM patients (Calip et al., 2016; Thakkar et al., 2013) or even decreased cancer risk (Häggström et al., 2017) compared to T2DM patients not using SUs. The conflicting data regarding the effects of SUs on cancer risk and development may be the result of differential effects of the individual SUs in terms of systemic or off-target effects.

The aim of this systematic review is to discuss the available preclinical and clinical evidence on differences in cancer risk and development between patients treated with different SU drugs. Understanding these so-called within-SU class differences is important to understand the conflicting data regarding cancer risk of SUs and to determine whether sufficient data is available to guide clinical selection of SUs for glycemic control. In addition, the accumulated preclinical and clinical evidence of the differential effects of SUs on cancer risk in T2DM patients may help to identify novel cancer treatment targets.

2. Search strategy

For clinical studies, databases including Medline (using PubMed), Cochrane, Database of Abstracts on Reviews and Effectiveness, and several trial registries (last search update March 21st, 2019, see supplementary file S1 for the complete search strategy) were searched for relevant meta-analyses, randomized trials, case-control studies and observational studies by two authors. Acetohexamide and tolazamide were excluded from the search, since these SUs are currently not registered in Europe or the United States of America. Studies that investigated cancer incidence in T2DM patients and compared individual SUs to each other were eligible for selection. Title and abstract were screened by two authors and full text articles were selected. See supplementary file S1 for detailed information on search strategy for clinical data and Fig. S1 for the flow chart of data extraction.

For preclinical data, separate searches were performed for the eight different SUs in Medline (using PubMed) combined with the terms "cancer OR tumor* OR tumour*". Based on the abstracts, relevant articles on the effects of SUs on cancer cell growth and intracellular mechanisms in preclinical models of cancer were selected by two authors. Relevant references of the selected articles were also searched. Articles written in languages other than English were excluded. Only original papers were included.

3. Differences between SUs in blood glucose lowering capacity

Increased glucose and insulin levels have cancer initiating and growth stimulatory effects in preclinical cancer models (Ariaans et al., 2015). Therefore, SUs that consistently normalize blood glucose levels with minimal systemic insulin exposure, e.g. by a specific meal dependent insulin release, are most likely to show benefit in terms of reducing relative cancer risk. SUs are grouped into three generations (Table 1), which differ with respect to strength of glucose-lowering capacity, side-effects and the presence of active metabolites. Target molecules for SUs are the sulfonylurea receptors, which are subunits of ATP-sensitive potassium channels (K^{+}_{ATP} channel) (Fig. 1) (Nichols, 2006). The different SUs have varying affinities for the sulfonylurea receptor isoforms and differ in hypoglycemia risk (Table 1). No severe hypoglycemia cases have been reported for gliclazide users, in contrast to the other SUs (Chan and Colagiuri, 2015; Holstein et al., 2010, 2001).

Extra-pancreatic blood glucose lowering effects of SUs in humans have also been described (Beck-Nielsen et al., 1988; DeFronzo and Simonson, 1984; Kolterman, 1987), however the available studies are small and not all SUs have been investigated, nor were different SUs compared within clinical studies. In dogs, glibenclamide was shown to have a lower extra-pancreatic blood glucose-lowering capacity than glimepiride (Müller et al., 1995). Postulated mechanisms for the extra-pancreatic effects include effects on hepatic glycogen metabolism, gluconeogenesis and lipogenesis. However, these mechanisms have mostly been studied at varying, often supra-physiological, drug concentrations and have not been studied in humans (Beck-Nielsen et al., 1988; Feldman and Lebovitz, 1969; Müller et al., 1995).

4. Differences between SUs in cancer risk: clinical evidence

The search strategy for the clinical studies yielded six eligible studies (Fig. S1) (Bo et al., 2013; Chang et al., 2012; Monami et al., 2007, 2009; Tuccori et al., 2015; Yang et al., 2010a), of which three retrospective (Bo et al., 2013; Monami et al., 2007; Tuccori et al., 2015) and three prospective (Chang et al., 2012; Monami et al., 2009; Yang et al., 2010a) (Table 2). All studies included patients with varying durations of diabetes and the mean follow-up periods ranged from 4.8 to 14 years. Five of the six studies focused on all-cancer incidence (Bo et al., 2013; Chang et al., 2012; Monami et al., 2007; Tuccori et al., 2015; Yang et al., 2010a) and one reported both all-cancer and site-specific cancer incidence (Monami et al., 2009). Two of the six studies had all-cancer mortality as primary outcome (Bo et al., 2013; Monami et al., 2007) and the other four had cancer incidence as primary outcome. Three of the six studies investigated dose-response relationships for individual SUs (Chang et al., 2012; Tuccori et al., 2015; Yang et al., 2010a) and one of the six studies investigated treatment duration-response differences for individual SUs (Monami et al., 2009). One study incorporated a time-varying design, taking changes in covariates during follow-up into account (Tuccori et al., 2015). In these six studies, data on cancer risk was found for gliclazide, glimepiride, glibenclamide and tolbutamide use; no data was found for the other SUs of interest (chlorpropamide and glipizide).

4.1. Gliclazide

Clinical evidence regarding effects of gliclazide use on cancer risk and development was described in three studies. In a retrospective observational study (n = 1277) with a mean follow-up of 14 years, T2DM patients treated with gliclazide had a lower cancer mortality risk (hazard ratio (HR) 0.30, 95% confidence interval (CI) 0.16–0.55) compared to glibenclamide treated patients (Bo et al., 2013). The analyses were adjusted for metformin and insulin use, age, sex, body-mass index (BMI), smoking, diabetes duration, anti-hypertensive therapy, glycated hemoglobin (HbA1c), presence of retinopathy, neuropathy and cardiovascular diseases.

The second study had a prospective design including 6103 patients and showed that 'ever use' compared to 'never use' of gliclazide was associated with a lower cancer risk (HR 0.65, 95%CI 0.49–0.83) in a dose dependent matter in the ever group (Yang et al., 2010a). Ever use was defined as use of gliclazide at, or within 2.5 years before, enrolment or during follow-up period. Outcomes were adjusted for age, sex, BMI, smoking, alcohol use, baseline HbA1c, systolic blood pressure, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, and ever use of statins, renin-angiotensin system inhibitors, metformin and insulin. This study did not correct for HbA1c levels of patients during follow-up.

The third study was a prospective, case-control study including 195 cases with cancer and 195 cases without cancer matched for age, sex, duration of diabetes, BMI, HbA1c, comorbidity, smoking and alcohol use (Monami et al., 2009). This study showed that T2DM patients using gliclazide for at least 12 months (odds ratio (OR) 0.39, 95%CI 0.21–0.74) and for at least 36 months (OR 0.40, 95%CI 0.23–0.69) had

Table 1

Mechanisms of action and hypoglycemia risks of SUs. HR: hazard ratio; K^+_{ATP} channels: ATP-sensitive potassium channels; OR: odds ratio; RR: relative risk; SUR: sulfonylurea receptor. *: study in patients aged 65 years or older; this is relevant because this patient group has a higher hypoglycemia risk than younger patients. §: HR, OR, and RR were all adjusted.

Sulfonylurea derivative	Generation	Mechanism of action (Arnouts et al., 2014; Gopalakrishnan et al., 2000; Proks et al., 2002)	Point of action	Hypoglycemia risk §
Acetohexamide	1	Increases pancreatic insulin secretion. Closes K^+_{ATP} channels located on β-cells.	SUR1 (Gopalakrishnan et al., 2000)	No reliable data
Chlorpropamide	1	Increases pancreatic insulin secretion. Closes K^+_{ATP} channels located on β-cells.	SUR1 (Gribble and Reimann, 2003)	Only as comparator group
Tolazamide	1	Increases pancreatic insulin secretion. Closes K^+_{ATP} channels located on β-cells. Increases peripheral insulin sensitivity.	SUR1 (Gopalakrishnan et al., 2000)	Versus chlorpropamide: RR 0.6 (0.4–1.0)* (Shorr et al., 1996)
Tolbutamide	1	Increases pancreatic insulin secretion. Closes K^+_{ATP} channels located on β-cells.	SUR1 (Proks et al., 2002)	Versus chlorpropamide: RR 0.2 (0.1–0.4)* (Shorr et al., 1996)
Glibenclamide	2	Increases pancreatic insulin secretion. Closes K^+_{ATP} channels located on β-cells.	SUR1 (Proks et al., 2002) SUR2A (Proks et al., 2002) SUR2B (Proks et al., 2002)	Versus other SUs: HR 1.83 (1.35–2.49) (Gangji et al., 2007) Versus metformin: HR 3.95 (3.66–4.26) (Leonard et al., 2018) Versus glipizide: HR 1.04 (0.18–6.85) (Andersen and Christensen, 2016) Versus chlorpropamide: RR 1.0 (0.8–1.3)* (Shorr et al., 1996) Incidence: 5.6/1000 (Holstein et al., 2001)
Glipizide	2	Increases pancreatic insulin secretion. Closes K^+_{ATP} channels located on β-cells.	SUR1 (Proks et al., 2002)	Versus metformin: HR 2.57 (2.38–2.78) (Leonard et al., 2018) Versus chlorpropamide RR 0.6 (0.4–0.9)* (Shorr et al., 1996)
Gliclazide	2	Increases pancreatic insulin secretion. Closes K^+_{ATP} channels located on β-cells.	SUR1 (Proks et al., 2002)	Versus other SUs: RR 0.47 (0.27–0.79) (Chan and Colagiuri, 2015) Versus glipizide: OR 0.22 (0.05–0.96) (Andersen and Christensen, 2016) Versus glimepiride OR 0.40 (0.13–1.27) (Andersen and Christensen, 2016) Versus glibenclamide: OR 0.21 (0.03–1.48) (Andersen and Christensen, 2016)
Glimepiride	3	Increases pancreatic insulin secretion. Closes K^+_{ATP} channels located on β-cells.	SUR1 (Proks et al., 2002) SUR2 (Proks et al., 2002)	Versus metformin: 3.28 (2.98–3.62) (Leonard et al., 2018) Versus glibenclamide: OR 0.51 (0.09–2.83) (Andersen and Christensen, 2016) Versus glipizide: OR 0.54 (0.18–1.64) (Andersen and Christensen, 2016) Incidence: 0.86/1000 (Holstein et al., 2001)

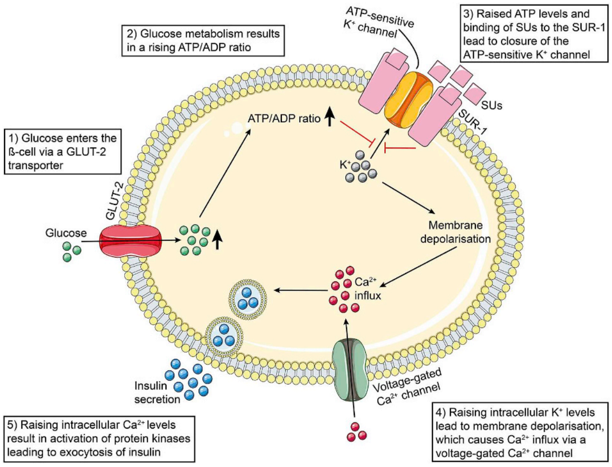
ATP-sensitive K⁺ channel
2) Glucose metabolism results in a rising ATP/ADP ratio
3) Raised ATP levels and binding of SUs to the SUR-1 lead to closure of the ATP-sensitive K⁺ channel
SUs
SUR-1
ATP/ADP ratio
1) Glucose enters the ß-cell via a GLUT-2 transporter
K⁺
GLUT-2
Glucose
Membrane depolarisation
Ca²⁺ influx
Insulin secretion
Voltage-gated Ca²⁺ channel
5) Raising intracellular Ca²⁺ levels result in activation of protein kinases leading to exocytosis of insulin
4) Raising intracellular K⁺ levels lead to membrane depolarisation, which causes Ca²⁺ influx via a voltage-gated Ca²⁺ channel

Fig. 1. Schematic representation of the mechanism of action of sulfonylurea derivatives (SUs) on a β-cell of the pancreas. ADP: adenosine diphosphate; ATP: adenosine triphosphate; Ca^{2+}: calcium; GLUT-2: glucose transporter 2; K^+: potassium; SUR-1: sulfonylurea receptor 1. The numbered boxes describe the mechanism of action of SUs in sequential order.

a lower cancer risk compared to patients who had never used gliclazide. The analyses were adjusted for other glucose lowering treatments. Due to the limited cohort sizes, no separate HRs for specific cancer types were calculated.

4.2. *Glibenclamide*

Clinical evidence regarding effects of glibenclamide use on cancer risk and development was described in four studies. The first study had a prospective design including 6103 patients and showed that 'ever use' compared to 'never use' was associated with a lower cancer risk (HR 0.67, 95%CI 0.51–0.89) in a dose-dependent manner in the ever group (Yang et al., 2010a). Ever use was defined as use of glibenclamide at, or within 2.5 years before, enrolment or during the follow-up period. Outcomes were adjusted for age, sex, BMI, smoking, alcohol use, baseline HbA1c, systolic blood pressure, LDL-cholesterol related risks, HDL-cholesterol, triglyceride, and ever use of statins, renin-angiotensin system inhibitors, metformin and insulin. This study did not correct for HbA1c levels of patients during follow-up.

In contrast, the second study described a retrospective analysis involving 52,600 SU-naïve T2DM patients starting SU use between 1 January 1988 and 31 July 2013 with a mean follow-up of 5.3 years (Tuccori et al., 2015). Glibenclamide use was not associated with a change in risk of developing cancer compared to other second generation SUs (HR 1.09, 95%CI 0.98–1.22) (Tuccori et al., 2015). However, for a high cumulative dose (> 1096 drug consumptions of the daily defined dose) of glibenclamide, a dose-dependent higher cancer risk was found compared to other second generation SUs (HR 1.27, 95%CI 1.06–1.51) (Tuccori et al., 2015). Results were adjusted for year of cohort entry, age, sex, BMI, smoking, alcohol use, HbA1c before study cohort entry, duration of treated diabetes before study cohort entry, ever use of other anti-diabetic drugs before study cohort entry (including first-generation SUs), and ever use of aspirin, statins and non-steroidal anti-inflammatory drugs. Strong points of this study were that both duration of SU use and the dose were taken into account, and a time-dependent analysis of exposure to SUs was incorporated.

Similarly, another study also described an association between glibenclamide use and higher cancer risk. This study was a prospective, case-control study including 195 cases with cancer and 195 cases without cancer matched for age, sex, duration of diabetes, BMI, HbA1c, comorbidity, smoking and alcohol use (Monami et al., 2009). This study showed that the OR for malignancies after exposure to glibenclamide for at least 12 and at least 36 months was 2.24 (95%CI 1.21–4.14) and

Table 2
Overview of selected clinical studies. DDD: daily defined dose; HbA1c: glycated hemoglobin; HR: hazard ratio; NR: not reported; OR: odds ratio; P: prospective; R: retrospective. All outcome measures presented in the table are adjusted values if provided. All studies presented in the table investigated any site of cancer.

Author	Design	Follow-up[c]	Size (n)	Diabetes duration[c]	Baseline HbA1c (%)	Specification of SU treatment	Comparator	Outcome
Bo et al., 2013	R	14.0 (NR)[b]	1277	9 (11)[a]	6.7 (1.2) [b]	Gliclazide Tolbutamide	Glibenclamide Glibenclamide	HR 0.30 (0.16–0.55) (Mortality) HR 0.48 (0.29–0.79) (Mortality)
Monami et al., 2007	R	5.0 (1.6)[b]	568	7.7 (5.1)[b], gliclazide 13.2 (10.6)[b], glibenclamide	7.4 (1.7)[b] 8.4 (2.0)[b]	Glibenclamide	Gliclazide	OR 3.6 (1.1–11.9) (Mortality)
Tuccori et al., 2015	P	5.3 (4.2)[b]	52,600	0.3 (0.9)[b], glibenclamide 1.3 (2.0)[b], other SUs	8.7 (2.9)[a] 8.5 (2.4)[a]	Glibenclamide Glibenclamide > 1096 DDD	Other 2nd generation SU Other 2nd generation SU	HR 1.09 (0.98–1.22) (Cancer risk) HR 1.27 (1.06–1.51) (Cancer risk)
Chang et al., 2012	R	7.4 (NR)[a]	108,920	3.6 (2.3) [b]	NR	SU (1st/2nd generation) SU (glimepiride)	Non-use of SUs Non-use of SUs	OR 1.08 (1.01–1.15) (Cancer risk) OR 1.00 (0.93–1.08) (Cancer risk)
Yang et al., 2010a	P	4.8 (2.4)[a]	6103	6 (9)[a], controls 8 (10)[a], cases	7.2 (2.0)[a] 7.4 (2.3)[a]	Ever glibenclamide Ever gliclazide	Never glibenclamide Never gliclazide	HR 0.67 (0.51–0.89) (Cancer risk) HR 0.65 (0.49–0.83) (Cancer risk)
Monami et al., 2009	P	6.5 (3.8)[b]	390	9.3 (10.4)[b], cases 9.3 (10.4)[b], controls	7.7 (1.7)[b] 7.7 (1.8)[b]	Glibenclamide (12 months) Glibenclamide (36 months) Gliclazide (12 months) Gliclazide (36 months)	Non-use of glibenclamide Non-use of glibenclamide Non-use of gliclazide Non-use of gliclazide	OR 2.24 (1.21–4.14) (Cancer risk) OR 2.62 (1.26–5.42) (Cancer risk) OR 0.39 (0.21–0.74) (Cancer risk) OR 0.40 (0.23–0.69) (Cancer risk)

[a] Median (interquartile range).
[b] Mean (standard deviation).
[c] In years.

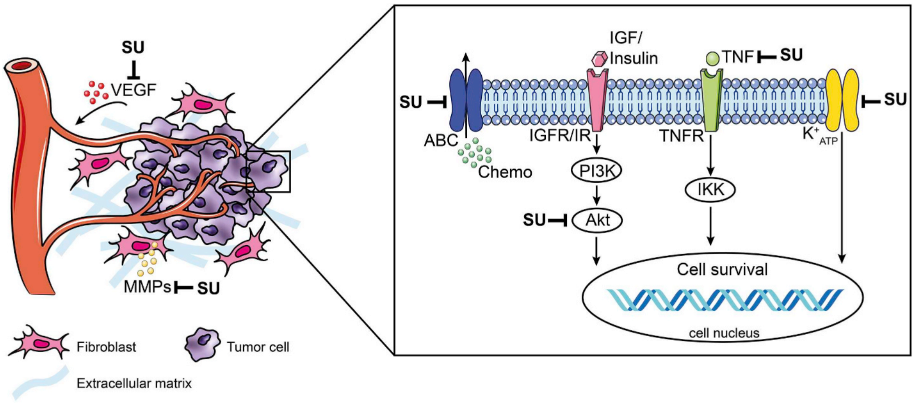

Fig. 2. Potential anti-cancer effects of sulfonylurea derivatives (SUs). ABC: adenosine triphosphate (ATP) binding cassette transporter; Akt: protein kinase B; Chemo: chemotherapy; IGF: insulin-like growth factor; IGFR: insulin-like growth factor receptor; IR: insulin receptor; IKK: I-kappaB-kinase; K^+_{ATP}: ATP-sensitive potassium channel; MMP: matrix metalloproteinase; PI3K: phosphoinositide 3-kinase; TNF: tumor necrosis factor; TNFR: tumor necrosis factor receptor; VEGF: vascular endothelial growth factor. SUs have been shown to inhibit VEGF *in vitro* and *in vivo* resulting in impaired vasculoneogenesis and angioneogenesis. Degradation of the extracellular matrix is impaired by the SU glibenclamide by inhibition of MMPs, which results in less proliferation and invasiveness of cancer cells. Sensitivity of cancer cells for chemotherapy might increase due to inhibited cellular export of chemotherapeutics as a result of inhibitory effects of the SU glibenclamide on ABC transporters. The SU chlorpropamide selectively inhibits the Akt pathway activity in cancer cells, resulting in cell growth arrest and apoptosis of cancer cells *in vitro* and *in vivo*. SUs have also been shown to inhibit TNF and TNFR levels in cancer cells, which might have pro-cell death effects. Inhibition of K^+_{ATP} by SUs reduces cancer cell growth *in vitro* and *in vivo*, possibly by inducing apoptosis.

2.62 (95%CI 1.26–5.42), respectively, compared to no exposure to glibenclamide (Monami et al., 2009). The analyses were adjusted for other oral glucose lowering treatments. The number of patients in this study is relatively small.

Lastly, a retrospective study (n = 568) with a mean follow-up of 5 years, described a higher all-cancer mortality in glibenclamide users compared to gliclazide users (OR 3.6, 95%CI 1.1–11.9) (Monami et al., 2007). This analysis was corrected for age, sex, BMI, insulin and metformin treatment. No dose response or cumulative duration analyses were performed and the analysis was not adjusted for HbA1c.

4.3. Glimepiride

In a case-control study, 108,920 newly diagnosed T2DM patients were identified (Chang et al., 2012). From this cohort, 8194 cancer cases and 32,776 age- and sex-matched diabetic controls with a mean diabetes duration of 3.6 years and a median follow-up of 7.4 years were included in the analyses (Chang et al., 2012). Use of glimepiride compared to 'non-use' did not increase overall cancer risk (OR 1.00, 95%CI 0.93–1.08) in newly-diagnosed diabetes patients (Chang et al., 2012). It is not clear whether the 'non-use' group included patients using no medication at all or patients not using glimepiride. The remaining non-glimepiride SUs were grouped together as first/second generation SUs and showed an increased cancer risk compared to 'non-use' (OR 1.08, 95%CI 1.01–1.15) (Chang et al., 2012). No dose-response or duration response relationships for any SUs were found (Chang et al., 2012). The analyses were adjusted for many covariates including insulin, SUs, glinides, metformin, thiazolidinediones, α-glucosidase inhibitors, statins, β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, aspirin, chronic liver disease, nephropathy, cerebrovascular disease, and chronic kidney disease. However, it was not described whether the analysis was also adjusted for other diabetes related covariates, for example HbA1c or BMI.

4.4. Tolbutamide

In a retrospective observational study (n = 1277) with a mean follow-up of 14 patients treated with tolbutamide had a lower cancer mortality compared to patients treated with glibenclamide (HR 0.48, 95%CI 0.29–0.79) (Bo et al., 2013). The analyses were adjusted for metformin and insulin use, age, sex, BMI, smoking, diabetes duration, anti-hypertensive therapy, HbA1c, presence of retinopathy, neuropathy and cardiovascular diseases.

4.5. Conclusions clinical evidence

In the majority of the studies described, gliclazide use was either associated with a lower risk of developing cancer (Monami et al., 2009; Yang et al., 2010a) or a lower risk of cancer-related mortality (Bo et al., 2013; Monami et al., 2007) compared to other SUs or never use. Moreover, one study showed that the reduced cancer risk in gliclazide users was dose-dependent (Yang et al., 2010a). The majority of studies point to a higher cancer risk and all-cancer mortality risk for glibenclamide users compared to T2DM patients using other SUs or never use and this effect was also dose-dependent (Bo et al., 2013; Monami et al., 2009, 2007; Tuccori et al., 2015). Only two studies directly compared SUs to one another (glibenclamide vs tolbutamide and glibenclamide vs gliclazide (Bo et al., 2013), and glibenclamide vs gliclazide (Monami et al., 2007)), confirming differences in cancer-related mortality of SUs. However, the evidence should be interpreted with caution since all studies included were either small and grouped all cancers together or did not account for duration or dose-response relationships. Grouping cancer types might introduce bias, since certain tissue types and malignancies may be more sensitive to effects of increased blood glucose and insulin levels. Furthermore, the methodology used in each study differed substantially; different study designs and different statistical analyses were used. All studies adjusted for potential confounders but to a varying degree. Importantly, all included studies corrected for at least metformin and insulin use. In case patients used other glucose lowering agents, the analyses were either corrected for or these patients were excluded from the study. It is uncommon to use two different SUs at the same time, so it is unlikely that the effect seen is influenced by concurrent SU use. Taking these limitations into account, T2DM patients using gliclazide may have a lower cancer risk and T2DM patients using glibenclamide may have a higher cancer risk than T2DM patients using other SUs.

5. Preclinical evidence of the effects and working mechanisms of SUs on cancer cells

To gain insight in possible systemic or off-target effects explaining the different clinical cancer risks of varying SUs, available evidence of growth inhibitory effects and potential anti-cancer mechanisms of SUs in preclinical models of cancer is discussed in this section. This evidence is summarized in Fig. 2. Most data are available for glibenclamide, which is frequently used in cell line models as a pharmacological tool to block transporters such as the potassium transporter channel. This provides data on *in vitro* effects of glibenclamide on cancer cell growth from studies not primarily designed to study SUs.

5.1. Effect of SUs on cancer cell growth

Glibenclamide inhibited growth of human prostate (Abdul and Hoosein, 2002a), hepatocellular (Kim et al., 1999; Malhi et al., 2000; Zhou et al., 2003), breast (Nunez et al., 2013; Woodfork et al., 1995), gastric (Qian et al., 2008), bladder (Wondergem et al., 1998), glioma (Ru et al., 2014) and colon (Abdul and Hoosein, 2002b) cancer cell lines *in vitro*. In human prostate, glioma and colon cancer cells this effect was dose-dependent and occurred at doses around 0.1 mM (50 μg/mL) (Abdul and Hoosein, 2002a, Abdul and Hoosein, 2002b; Ru et al., 2014), which is at least 100 fold higher than the plasma concentrations achieved clinically in daily practice with doses used in T2DM patients (Coppack et al., 1990). In bladder and breast cancer cells, reduced cellular proliferation has also been reported to be dose-dependent and was seen at concentrations which did not differ greatly from clinically achievable plasma concentrations (Wondergem et al., 1998; Woodfork et al., 1995). In human ovarian cancer cell line models, cell growth was not inhibited by glibenclamide (Han et al., 2007; Zhanping et al., 2007). Proliferation of glioma cells was inhibited by 7 days tolbutamide treatment at 100 μM (Huang et al., 2009), this is about 2600 times the clinically achievable range of tolbutamide plasma concentrations (Andreasen and Vesell, 1974).

Glipizide, but not glimepiride, suppressed tumor growth and metastases *in vivo* in breast cancer and melanoma xenografts and in transgenic mouse models of breast cancer (Qi et al., 2014). The doses of glipizide and glimepiride used in the study resulted in concentrations consistent with clinically achievable plasma concentrations (Simonson et al., 1997).

In general, it appears that in certain conditions, treatment with glibenclamide can reduce growth of cancer cells. However, in the majority of studies only one or two cancer cell lines were studied and glucose concentration of cell culture media used varied widely or were not mentioned. No studies compared the influence of glibenclamide on cell growth in a large range of different cell lines in the same conditions. Furthermore, the potential mechanisms of growth inhibition of glibenclamide are not elucidated. Therefore, the results should be interpreted with caution and effects and mechanisms may be cell line specific. The possible mechanisms by which SUs might influence cancer development are discussed in the following paragraphs.

5.2. Effects of SUs on growth factors and growth factor pathways

Insulin and insulin-like growth factor (IGF) have been shown to stimulate cancer cell proliferation. Exposing a human neuroblastoma cell line to glibenclamide resulted in an increase of mRNA expression of insulin and IGF-1 receptors (Ota et al., 1989). This resulted in increased binding of insulin and IGF-1 to the neuroblastoma cells, but not in increased glucose uptake. Only short-term experiments, up to 24 h duration, were described. Studies with longer drug incubation times are required to determine whether this results in enhanced cancer cell growth.

Gliclazide inhibited levels of tumor necrosis factor (TNF) production by human peripheral blood mononuclear cells and inhibited TNF bioactivity and immunoreactivity in mouse serum (Desfaits et al., 1998; Fukuzawa et al., 1999; Qiang et al., 1998). Chlorpropamide inhibited levels of TNF receptors in peripheral blood mononuclear cells (Nunes et al., 2004). TNF is a cytokine, which can have both pro-survival and pro-cell death effects, mediated through the TNF receptors. More detailed mechanistic studies are required to determine how different SUs influence this delicate balance in cancer cells.

The protein kinase B (Akt) pathway is a signaling pathway, often activated in cancer and downstream of the insulin receptor. This pathway is involved in many cellular processes, including cell survival, cell cycle progression and cellular growth (Fresno Vara et al., 2004). A chlorpropamide analogue API-2 selectively inhibited the Akt pathway activity in cancer cells with elevated Akt expression without influencing other pathways, resulting in cell growth arrest and apoptosis of cancer cells *in vitro* and *in vivo* (Yang et al., 2004). This is of interest since the Akt pathway is hyperactivated in many cancer types and therefore an attractive therapeutic target. However, clinical development of such inhibitors has been hampered by drug-toxicity (Mundi et al., 2016).

5.3. Effects of SUs on ATP-binding cassette transporters and solute channels

Sulfonylurea receptors belong to the ATP-binding cassette transporter superfamily, which are transmembrane proteins that transport substrates across cellular membranes. Multidrug-resistance proteins (MRPs) are ATP-binding cassette transporters involved in the cellular export of several drugs, including chemotherapeutic drugs, and can therefore protect cancer cells from anti-cancer drugs (Lautier et al., 1996). Glibenclamide is an inhibitor of various ATP-binding cassette transporter proteins (Golstein et al., 1999; Hamon et al., 1997; Sheppard and Robinson, 1997; Stieger et al., 2000). Glibenclamide inhibited MRP1 in human lung cancer cells resulting in enhanced sensitivity of these cells to the anti-cancer drug and MRP substrate vincristine (Payen et al., 2001). However, in this study, the dose of glibenclamide required for this effect was at least 10-fold higher than the therapeutic plasma concentration currently achieved clinically (Coppack et al., 1990). Glibenclamide also inhibited the transport of the drug alpha-tocopheryl-phosphate across the cell membrane into cells in a leukemia cell line, thereby reducing the anti-proliferative effect of this drug (Negis et al., 2007). However, the transporter involved was not identified. If this effect is indeed confirmed at physiological doses for certain drug transporters then caution may be required when glibenclamide use is combined with anti-cancer drugs. However, although the efficacy of efflux pump inhibitors to improve the effect of chemotherapeutics has been extensively studied clinically, results have so far been disappointing (Ughachukwu and Unekwe, 2012).

Some potassium channels are regulated by sulfonylurea receptors and can be (potently) inhibited by, for example, glibenclamide (Burke et al., 2008; Reeve et al., 1992; Zhou et al., 2003). Deregulated expression of all four classes of potassium channels has been demonstrated in human cancers and overexpression has been correlated with increased cell proliferation (Hemmerlein et al., 2006; Huang and Jan 2014; Pardo and Stuhmer, 2008; Wang, 2004). Pharmacological inhibition of potassium channels has been shown to reduce cancer cell growth *in vitro* and *in vivo* in cancers with overexpression of these channels (Downie et al., 2008). Voltage-gated potassium channels were blocked by glibenclamide in a hepatocellular carcinoma cell line, resulting in reduced proliferation (Zhou et al., 2003). However, in another study, no effect was seen in an ovarian cancer cell line (Zhanping et al., 2007). Potassium channel blockers mediate depolarization of membranes; this can result in programmed cell-death (apoptosis) and therefore this may also be expected for SUs. Indeed, induction of apoptosis by glibenclamide was described in several human cancer cell line models (Abdul and Hoosein, 2002a; Kim et al., 1999; Qian et al., 2008; Ru et al., 2014; Suzuki et al., 2012; Yan et al., 2017). In addition, both glibenclamide and tolbutamide enhanced apoptosis induced by other drugs (Mohapatra et al., 2009; Paíno et al., 2010). In contrast, gliclazide protected cancer cells from hydrogen peroxide induced apoptosis (Kimoto et al., 2003; O'Brien et al., 2000; Sliwinska et al., 2012). In general, it appears that influence of glibenclamide on potassium channels and apoptosis is likely to be dose dependent and potentially cell-line dependent.

5.4. Effects of SUs on angiogenesis and metastasis

Angiogenesis plays a major role in cancer progression and metastasis, and is mediated by growth factors such as vascular endothelial growth factor (Gu et al., 2015). Inhibition of neovascularization can be useful as anti-cancer therapy by controlling tumor growth and metastasis. Bevacizumab, a monoclonal anti-body against vascular endothelial growth factor A, and several tyrosine kinase inhibitors with anti-angiogenic properties are registered as anti-cancer therapy in selected tumor types.

Glibenclamide inhibited cellular invasion and migration in a human ovarian cancer cell line model through inhibition of components of the angiogenic pathway (Yasukagawa et al., 2012). *In vivo* studies in early chick embryo chorioallantoic membrane and yolk sac membrane models and in prostate cancer mouse models showed that glipizide also inhibited vasculoneogenesis and angioneogenesis (Gu et al., 2015; Qi et al., 2016, 2014).

Degradation of the extracellular matrix is essential for tumor invasion and metastasis. Among the essential proteins for this process of degradation are various types of matrix metalloproteinase. Growth, proliferation and invasiveness of breast cancer in TA2 mice was inhibited by a combined treatment of glibenclamide and cobalt chloride through inhibition of matrix metalloproteinases (Rong et al., 2013). In contrast, in ovarian cancer cells, glibenclamide had no effect on cell adhesion, cell invasion or migration (Li et al., 2009). Lymphatic spread is frequently a first step in cancer metastasis. Acetohexamide dose-dependently inhibited breast cancer intravasation into lymph ducts in a three-dimensional cell co-culture assay (Kretschy et al., 2013). This effect of acetohexamide was identified during a screening procedure of hundreds of drugs registered for non-cancer indications. This observation is yet to be confirmed in other *in vitro* and *in vivo* cancer models and the exact mechanism has not been elucidated.

5.5. *The effects of SUs on anti-cancer treatment*

SUs might not only affect cancer initiation and progression but also the efficacy of anti-cancer treatment. Glibenclamide has been shown to protect human glioblastoma, primary astrocytes and normal lung tissue cell lines from radiation-induced cell death (Jiang et al., 2009). Mice injected with glibenclamide before total body irradiation lived longer compared to mice injected with glibenclamide after radiation therapy or without glibenclamide treatment (Jiang et al., 2009). The specific underlying mechanisms of the radio-protective effect of glibenclamide pre-administration are unknown (Jiang et al., 2009). Furthermore, in liver and lung cancer cell lines glibenclamide has been shown to increase the cytotoxicity of the chemotherapeutic drug doxorubicin (Subramaniyam et al., 2018). This study showed altering DNA conformation effects of glibenclamide possibly explaining its synergistic effects on doxorubicin treatment (Subramaniyam et al., 2018).

Analogues of chlorpropamide inhibited human aldehyde dehydrogenase 3 (ALDH-3) in cancer cells and sensitized breast cancer cells to chemotherapy (Rekha et al., 1998; Sládek et al., 2001). ALDH-3 can be overexpressed in cancer cells and is involved in detoxification of certain types of chemotherapy and may therefore be involved in resistance to these therapies. Thus, inhibition of ALDH-3 is of interest to enhance tumor sensitivity to these chemotherapeutic drugs, however this has yet to be investigated in *in vivo* models.

Cancer cell resistance to chemo- and radiotherapy is, among others, enhanced by upregulation of the Akt-pathway (Shimura et al., 2014; Yang et al., 2010b). A chlorpropamide analogue, API-2, inhibited this pathway and reduced chemo- and radioresistance (Shimura et al., 2014; Williams et al., 2012; Yang et al., 2010b). Furthermore, API-2 sensitized immune resistant tumors for $CD8^+$ T-cell mediated apoptosis by Akt inhibition and might therefore improve immunotherapy (Noh et al., 2009). API-2 can induce either apoptosis or metastasis depending on the nuclear β-catenin expression, which differs between cancer cells suggesting pleiotropic effects of API-2 (Tenbaum et al., 2012). It is unknown whether use of chlorpropamide itself results in the same effects.

The preclinical evidence suggests numerous potential anti-cancer mechanisms of SUs. However, systemic studies in cancer cell line panels and relevant model systems at clinically achievable drug concentrations are lacking.

6. Discussion

The overall clinical evidence suggests that the influence of SUs on cancer risk in T2DM patients differs between the various SUs. Potential mechanisms include differing affinities for the sulfonylurea receptors resulting in differential systemic insulin exposure and off-target anti-cancer effects mediated for example through potassium transporters or drug export pumps.

Observational studies demonstrated that the use of the second generation SU gliclazide was associated with a lower risk of developing cancer compared to never use of gliclazide (Monami et al., 2009; Yang et al., 2010a). Gliclazide users also had a lower risk of cancer-related mortality compared to glibenclamide users (Bo et al., 2013; Monami et al., 2007). Glibenclamide use was associated with a higher risk of developing cancer compared to other second generation SUs and to no use of glibenclamide (Monami et al., 2009; Tuccori et al., 2015). All studies had important methodological limitations and used different study designs and statistical methods. Interpretation of results and direct comparisons of the retrospective clinical studies were hampered by low numbers of cancer cases, grouping together of different cancer types and lack of data on dose or cumulative exposure of SUs.

Higher insulin levels have tumor promoting effects *in vitro* in cell line models, *in vivo* in animal models and in human epidemiological studies (Ariaans et al., 2015). Metformin reduces peripheral insulin resistance resulting in lower blood insulin and glucose levels (Fig. 3). This could, at least in part, explain the potential anti-cancer effects of this drug (Jalving et al., 2010; Soranna et al., 2012). The different effects of gliclazide and glibenclamide on cancer risk and mortality may also be explained by differential influences on blood insulin levels of both agents (Fig. 3). Glibenclamide has been associated with an increased and pro-longed hypoglycaemia risk compared to other SUs. This can be explained by the relatively long half-life time of glibenclamide due to high affinity for the sulfonylurea receptor 1 and the slow reversibly of the sulfonylurea receptor 1 binding (Gribble and Reimann, 2003b; Melander, 2004). The accumulation of active metabolites due to impaired renal function may also contribute to the hypoglycaemia risk of glibenclamide (Arnouts et al., 2014; Gangji et al., 2007; Harrower, 2000). Glibenclamide is not selective for just sulfonylurea receptor 1 located on the pancreatic β-cells of the pancreas, but also binds sulfonylurea receptor 2A and B which are widely expressed, amongst others, on cardiac muscle (Gribble and Reimann, 2003b; Seino et al., 2012). In contrast, gliclazide binds more selectively with rapid reversibility to sulfonylurea receptor 1 located on pancreatic β-cells (Gribble and Reimann, 2003b; Seino et al., 2012) and is hepatically metabolised into inactive metabolites before renal elimination (The electronic Medicines Compendium, n.d.).

SUs with the most selective meal dependent insulin release are expected to be associated with the lowest cancer risks due to lower overall insulin exposure and this may explain the observed clinical differences. Differential insulin responses of glibenclamide and gliclazide have indeed been demonstrated. The physiological pancreatic insulin response is biphasic, the first phase concerns rapid insulin exocytosis within 5–10 min after stimulation whereas the second phase can sustain for hours in case of persisting elevated glucose levels (Wang and Thurmond, 2009). In an *in vitro* model measuring insulin release in isolated rat pancreases, a biphasic insulin response to gliclazide treatment was demonstrated which was in contrast to the delayed monophasic insulin response to glibenclamide treatment (Gregorio et al., 1992). In two small randomized double-blind trials, containing 24 and 12 patients respectively, glibenclamide was shown to have a stimulatory effect on the second but not on the first phase of insulin secretion (Cozma et al., 2002; Ligtenberg et al., 1997). Furthermore, inappropriate insulin secretion in case of low blood glucose levels has been shown in T2DM patients and healthy volunteers using glibenclamide (Draeger et al., 1996; Hollander et al., 2001; Riefflin et al., 2015; Szoke et al., 2006). The biphasic glucose-dependent insulin

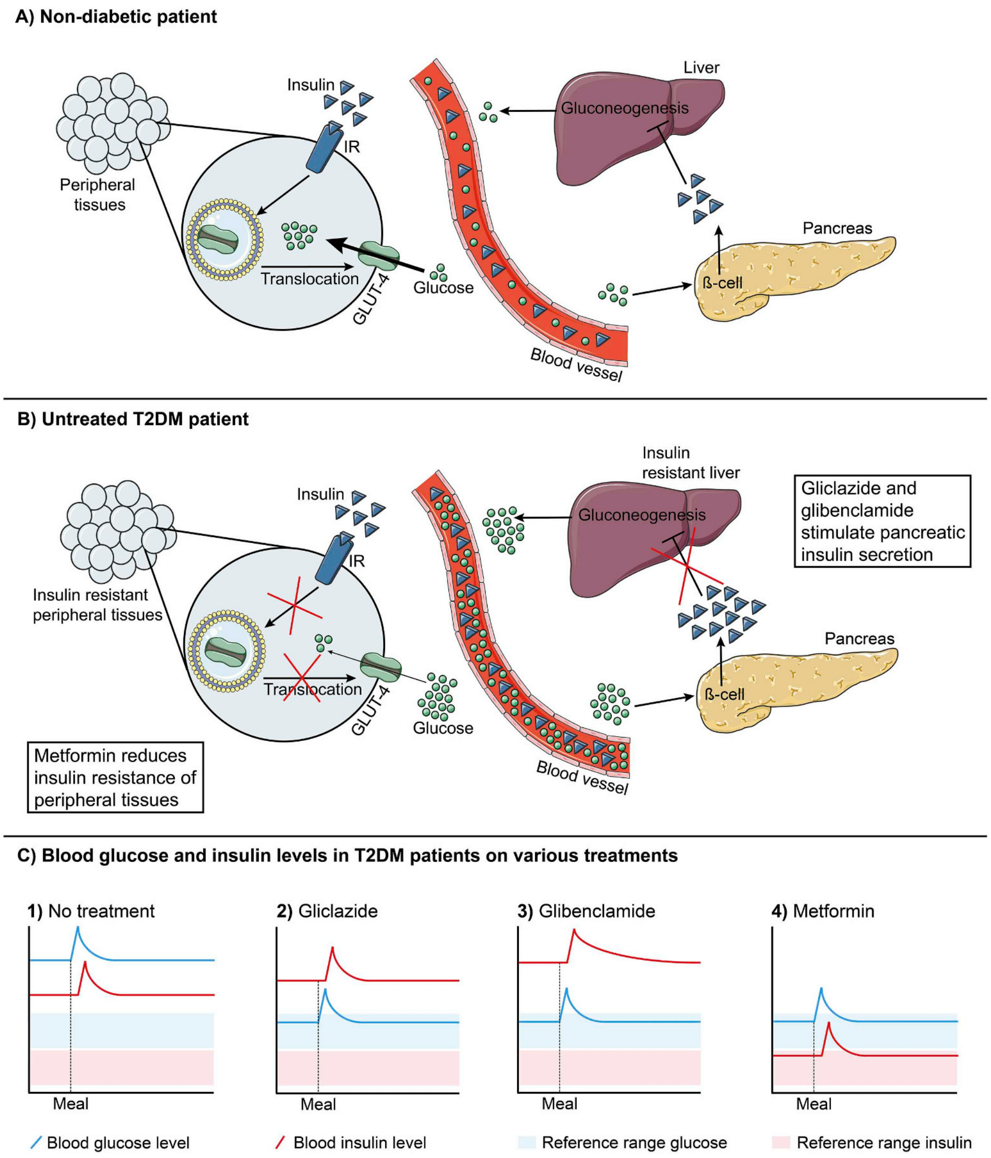
A) Non-diabetic patient
Liver
Insulin
IR
Gluconeogenesis
Peripheral tissues
Pancreas
Translocation
GLUT-4
Glucose
ß-cell
Blood vessel
B) Untreated T2DM patient
Insulin resistant liver
Gliclazide and glibenclamide stimulate pancreatic insulin secretion
Insulin
Gluconeogenesis
IR
Insulin resistant peripheral tissues
Pancreas
Translocation
GLUT-4
Glucose
ß-cell
Metformin reduces insulin resistance of peripheral tissues
Blood vessel
C) Blood glucose and insulin levels in T2DM patients on various treatments
1) No treatment
2) Gliclazide
3) Glibenclamide
4) Metformin
Meal
Meal
Meal
Meal
Blood glucose level
Blood insulin level
Reference range glucose
Reference range insulin

Fig. 3. Schematic representation of blood insulin and glucose interactions in relation to oral glucose lowering agents. GLUT-4: glucose transporter 4; IR: insulin receptor; T2DM: type 2 diabetes mellitus. **A)** In non-diabetic patients, binding of insulin to peripheral tissues leads to translocation of glucose transporter 4 (GLUT-4) to the cell membrane enabling glucose influx. Glucose stimulates insulin excretion by β-cells of the pancreas. Insulin inhibits gluconeogenesis by the liver. **B)** In T2DM patients, peripheral tissues and liver tissue are insulin resistant. This results in hyperglycemia due to reduced cellular influx of glucose, increased insulin secretion by β-cells of the pancreas and stimulation of gluconeogenesis. **C1)** T2DM patients suffer from hyperglycemia and hyperinsulinemia. **C2)** Gliclazide treatment results in a slightly higher basal blood insulin level than in untreated T2DM patients and in a selective glucose-dependent insulin release. **C3)** Glibenclamide results in a less specific glucose-dependent insulin release than gliclazide, resulting in higher basal blood insulin levels and prolonged insulin secretion after a meal. **C4)** Metformin reduces insulin resistance of peripheral tissues and liver tissue resulting in less insulin secretion.

response of gliclazide was confirmed in four diabetic patients and four healthy controls (Chiasson et al., 1991). In conclusion, gliclazide appears to result in a selective glucose dependent insulin release which in turn results in a more physiological insulin response and a corresponding lower average blood insulin level than for example glibenclamide (Fig. 3).

Preclinical studies suggest that SUs could have direct inhibitory effects on cancer cell growth (Abdul and Hoosein, 2002a, Abdul and Hoosein, 2002b; Kim et al., 1999; Malhi et al., 2000; Nunez et al., 2013; Qian et al., 2008; Ru et al., 2014; Wondergem et al., 1998; Woodfork et al., 1995; Zhou et al., 2003). Especially glibenclamide had anti-proliferative effects in some preclinical cancer models, potentially through blockade of potassium channels thus inducing apoptosis (Abdul and Hoosein, 2002a, Abdul and Hoosein, 2002b; Golstein et al., 1999; Hamon et al., 1997; Kim et al., 1999; Malhi et al., 2000; Nunez et al., 2013; Qian et al., 2008; Ru et al., 2014; Sheppard and Robinson, 1997; Stieger et al., 2000; Wondergem et al., 1998; Woodfork et al., 1995; Zhou et al., 2003). However, glibenclamide is often studied due to its pharmacological effect on the potassium channels and not systematically with the goal of studying the anti-cancer effects of the drug. No large systematic comparison of growth inhibitory effects of the different SUs in panels of cancer cell lines have been performed. Furthermore, thorough investigation of effects of SUs on signal-transduction routes important to cancer cell growth have not been performed, and no studies on cancer cell metabolism were identified. Extra-pancreatic, organ specific effects of SUs on glucose metabolism exist and may differ between individual SUs as has been described for glibenclamide and glimepiride (Beck-Nielsen et al., 1988; Feldman and Lebovitz, 1969; Müller et al., 1995). The anti-cancer effects of SUs may be considered a novel extra-pancreatic effect. There is insufficient data available to determine whether the anti-cancer effects of SUs are correlated to their known extra-pancreatic effects on glucose metabolism.

The reported concentrations of SUs used in the reviewed *in vitro* studies appear to be high compared to the achievable therapeutic range in patients, which is measured as total (free plus protein-bound) plasma concentrations. Several factors complicate interpretation of these reported *in vitro* concentrations. Firstly, SUs bind to proteins in the cell culture medium (Hsu et al., 1974; Proks et al., 2018; Seedher and Kanojia, 2009, 2008) and, therefore, the actual free drug concentration available at the target may be lower than the reported SU concentration. Consequently, it is unknown at which actual drug concentrations the described anti-cancer effects of SUs at the cellular levels occurred. Secondly, SU binding affinities to albumin used for cell culture versus human albumin differ and SUs may bind to other proteins than only albumin (Proks et al., 2018). Thus translation of the *in vitro* data is seriously hampered due to the probable differing degrees of protein binding between *in vitro* models and patients. Furthermore, there are multiple factors besides protein binding that determine the free drug concentrations surrounding the therapeutic target in the tumor in patients (Smith et al., 2010).

Clinical and preclinical data are conflicting regarding influence of glibenclamide on cancer risk and development. This is likely due to differential systemic versus intra-cellular effects of SUs. The association of glibenclamide use and increased cancer risk may be explained by the relatively high insulin exposure during glibenclamide treatment compared to other SUs. This is clearly not compensated by cancer inhibiting effects at the cellular level in patients. The preclinically described potential anti-cancer effects of SUs are of interest from a mechanistic point of view and deserve further investigation. This may result in novel anticancer drug targets and/or potential repurposing of SUs.

In conclusion, it appears that T2DM patients using gliclazide may have a lower cancer risk than those using glibenclamide. However, the evidence on differences in cancer risk between the different SUs and SU classes is, at this time, not strong enough to guide clinical decision-making.

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Conflicts of interest

The authors have declared that no conflicts of interest exist.

Appendix A. Supplementary data

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