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# Are Sulfonylureas Less Desirable Than DPP-4 Inhibitors as Add-on to Metformin in the Treatment of Type 2 Diabetes?

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**Abstract** Sulfonylureas (SUs) are commonly used as add-on to metformin in treatment of type 2 diabetes in patients who are insufficiently controlled by metformin alone. They have good efficacy and have been shown to prevent microvascular complications. However, treatment with SUs is also associated with a high frequency of hypoglycemia, increased body weight, and a high risk of secondary failure. During recent years, dipeptidyl peptidase-4 (DPP-4) inhibitors have emerged as alternatives to SUs. They show similar efficacy as SUs but with lower risk of hypoglycemia, and reduction or no change in body weight, and if confirmed in humans, they may preserve islet function and thereby minimize the risk for secondary failure. Their limitation at present is the lack of long-term (>5 years) experience on durability and safety. Overall, therefore, the conclusion emerges that SUs are less desirable than DPP-4 inhibitors in management of hyperglycemia in type 2 diabetes.

**Keywords** Diabetes · Hyperglycemia · Sulfonylureas · Glimepiride · Glipizide · DPP-4 inhibitors · Vildagliptin · Sitagliptin · Saxagliptin · Islet function · Insulin secretion · Glucagon secretion · Hypoglycemia · Safety · Durability · Comparison

## Introduction

Targeting the hyperglycemia is of key importance in management of type 2 diabetes because lowering glycemia reduces both acute symptoms and the increased risk for retinopathy, nephropathy, and neuropathy [1]. Treating hyperglycemia may also improve the increased cardiovascular (CV) risk in type 2 diabetes, although this needs a multifactorial approach [2].

The key defect underlying hyperglycemia in type 2 diabetes is islet dysfunction, which has three components: 1) impaired insulin secretion (ie, insufficiently increased insulin secretion to match insulin resistance [3]); 2) defective suppression of glucagon secretion, which results in hyperglucagonemia and increased hepatic glucose production [4]; and 3) reduced islet cell mass [5]. These defects are early phenomena and are seen already several years before the diabetes diagnosis [6].

Treatment guidelines from national and international bodies have presented algorithms for sequential introduction of pharmacologic agents to treat the hyperglycemia [7–10]. The first-line pharmacologic agent is, for most patients, metformin, which mainly improves insulin sensitivity. In many patients, however, this is insufficient to reach target for glycemic control and a second agent is then suggested to be added. Sulfonylureas (SUs) have for a long time been recommended as this second treatment. During recent years dipeptidyl peptidase-4 (DPP-4) inhibitors have emerged as a new class of therapeutic agents [11]. These agents seem to be equally effective in improving glycemia as SUs but lack some of the negative effects of SUs. It may therefore be discussed whether DPP-4 inhibitors are more desirable than SUs as add-on to metformin in patients with inadequate glycemic control.

## Sulfonylureas

### History

SUs were developed as agents stimulating insulin secretion based on incidental finding of hypoglycemia during

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treatment with sulfonamides in the 1940s [12]. Their introduction in the treatment during the 1950s represented the first reliable oral treatment of diabetes. Since then, several SUs have been of key and central value in the treatment. Following the first (chlorpropamide, acetohexamide, and tolazamide) and second generations (tolbutamide), the third-generation SUs (glibenclamide [glyburide], gliclazide, glipizide, and glimepiride) are the most commonly used SUs today [13, 14].

## Mechanisms

SUs stimulate insulin secretion by activating β-cell SU receptors 1 (SUR1), closing ATP-dependent potassium channels (Kir6.2 channels), thereby inhibiting potassium flow across the plasma membrane [15]. This results in depolarization, which opens voltage-sensitive calcium channels, allowing uptake of extracellular calcium, increased cytosolic calcium, and exocytosis of insulin-containing granules. Importantly, this effect is glucose independent (ie, SUs stimulate insulin secretion both at low and high glucose concentrations).

SUR1 receptors also are expressed in the glucagon-producing islet α cells, and the net effect of Kir6.2 channel closure in these cells is a stimulation of glucagon secretion [16]. A stimulation of glucagon secretion by SUs has also been observed in humans with insulin deficiency in type 1 diabetes [17]; when insulin secretion is maintained, it may counteract the effect of SUs on α cells, which therefore may be difficult to observe. SUs may also reduce β-cell mass, through apoptosis [13]. Therefore, SUs do not sufficiently target the pathophysiologic defects of the disease: they stimulate insulin secretion, but they do so in a glucose-independent manner, they stimulate rather than inhibit glucagon secretion, and they tend to reduce rather than to increase β-cell mass.

## Clinical Effects

There is an extensive experience of antidiabetic efficacy by SUs [18]. Thus, SUs result in robust and marked initial reductions in hemoglobin $A_{1c}$ ($HbA_{1c}$), which is most evident after 6 to 12 months of therapy, when $HbA_{1c}$ usually is reduced by approximately 0.5% to 2%. Furthermore, SUs are in general well tolerated with few adverse events (apart from hypoglycemia and weight gain) and the price for SUs is low.

SUs have also been demonstrated to reduce the risk for microangiopathy in type 2 diabetes, as evident in the UKPDS (United Kingdom Prospective Diabetes Study) over a 10-year study period [1]. In contrast, whether SUs also reduce the risk of CV disease in type 2 diabetes has been a matter of discussion. The first long-term study examining this possibility, the UGDP (University Group Diabetes Program) study, showed an increased CV risk in patients treated with SUs [14]. It should be emphasized that it was tolbutamide that was used in this study and, therefore, the results are less valuable for the present-day SUs. However, later studies have also not been able to convincingly show that SUs may improve CV outcome. For example, in the UKPDS there was a trend, as 16% reduction in nonfatal myocardial infarction was observed in patients treated with SUs, but this was not significant [1]. Similarly, intense treatment with gliclazide resulted in a nonsignificant reduction in major macrovascular events in another study [19]. Furthermore, a retrospective cohort analyses has shown an excess of mortality and congestive heart failure in patients treated with SUs [20].

The reason why the improved glycemia by SUs does not seem to be associated with reduced CV risk, in spite of improving glycemia, is not known, but two aspects may be important: 1) SUs may have direct effects on SU 2A (SUR2A) and SU 2B (SUR2B) receptors expressed in cardiomyocytes and heart smooth muscle cells, which might have negative effects [21]. 2) Treatment with SUs is associated with hypoglycemia, which is proarrhythmogenic and may increase CV events [22, 23].

## Limitations

A limitation with SUs is a high rate of hypoglycemia. This is mainly because SUs also stimulate insulin secretion when glucose levels are low. It is difficult to estimate the risk for hypoglycemia during SU treatment because many events go undetected. In the UKPDS, the annual risk for hypoglycemia in patients treated with glibenclamide was 18% during 10 years [1]. A recent study based on self-reporting showed that the risk for severe hypoglycemia in patients treated with SUs was 7% [24]. Furthermore, an observational study found that more than 30% of patients treated with SUs have experienced hypoglycemia during the last 6 months and 4% have experienced severe hypoglycemia [25]. Other studies have reported that SUs are associated with a risk of 0.24 to 1.23 severe hypoglycemic events per 100 person-years, with a lower risk with the third-generation SUs than with the older SUs [26].

One implication of hypoglycemia is severe symptoms, which may need assistance of a third party and emergency assistance in hospitals. It was recently estimated that more than 5,000 patients each year experience severe hypoglycemia requiring emergency assistance only in the United Kingdom [26]. Furthermore, patients who experience hypoglycemia often fear a tight glycemic control of the disease, which may have implications for quality of life and the treatment to target. Moreover, hypoglycemia is associated with increased risk for CV diseases because it is

proarrhythmogenic [22], which might explain increased mortality during intense glucose control with compounds associated with high risk of hypoglycemia [23].

A second limitation with SUs is weight gain. This is seen in most patients and is usually within a 1- to 3-kg range [27]. The mechanism is not known but may be related to the hyperinsulinemia caused by SUs, as insulin is a trophic and anabolic hormone. However, it may also occur due to increased food intake to defend against frequent hypoglycemia induced by SUs. Regardless of the reason, the consequences of increased body weight are worsened insulin resistance and further increased CV risk.

A third limitation with SUs is that glucose control often deteriorates in spite of continuous treatment [28]. This is common for several different treatments but particularly characteristic for SUs. Secondary SU failure may be related to β-cell desensitization and/or to β-cell apoptosis induced by SUs [29]. Secondary failure is associated with worsening of the glycemic control.

## DPP-4 Inhibitors

### History

The antidiabetic action of DPP-4 inhibitors is based on the incretin hormone glucagon-like peptide-1 (GLP-1) [30]. GLP-1 is a 30 amino acid peptide that is produced in the small intestine and is released after meal ingestion. Together with GIP (glucose-dependent insulinotropic polypeptide), it is responsible for the incretin effect (ie, the augmentation of glucose-stimulated insulin secretion that is seen after meal ingestion). GLP-1 activates G-protein–coupled receptors in the pancreatic β cells, which raises cyclic AMP [31]. This results in a glucose-dependent stimulation of insulin secretion. GLP-1 may also increase β-cell mass through neogenesis and proliferation and inhibited apoptosis, as shown in rodents [32] and it inhibits glucagon secretion [4]. GLP-1 also inhibits gastric emptying and induces satiety, which add to the effects that are of potential value in the treatment of type 2 diabetes [30].

In the early 1990s, it was suggested that GLP-1 might be a potential target in the treatment of type 2 diabetes [33]. However, native GLP-1 is rapidly inactivated by the enzyme DPP-4 [11], which makes GLP-1 unsuitable for use in therapy. Two strategies to take advantage of the effects of GLP-1 were instead explored: 1) the use of GLP-1 receptor agonists, which are largely resistant to the action of DPP-4, and 2) the use of inhibitors of DPP-4, which prevent the inactivation of endogenous GLP-1 [11].

The proof-of-concept study showing that DPP-4 inhibition reduces glycemia in type 2 diabetes was published in 2002 [34]. Several DPP-4 inhibitors have now been developed and are in different stages in clinical development. Sitagliptin, vildagliptin, and saxagliptin have been approved in many countries worldwide. Linagliptin and alogliptin are in late clinical development (alogliptin has been approved in Japan) [35–39].

### Mechanisms

As shown for vildagliptin and sitagliptin, DPP-4 inhibitors stimulate insulin secretion and inhibit glucagon secretion [35, 36]. These effects are glucose dependent, which means that they vanish when glucose levels drop. Furthermore, a recent study also showed that vildagliptin reduces insulin secretion and sustains glucagon secretion during hypoglycemia (2.5 mmol/L), verifying the glucose dependency [40•]. This suggests that this treatment minimizes the risk for hypoglycemia. Furthermore, DPP-4 inhibition increases β-cell mass, as demonstrated in animal models of diabetes [41], although no such information is available in humans. Therefore, DPP-4 inhibitors target several key islet defects in type 2 diabetes: they stimulate insulin secretion in a glucose-dependent manner, they inhibit glucagon secretion, and they have a potential of increasing β-cell mass.

### Clinical Effects

All DPP-4 inhibitors in clinical use or in late clinical development reduce $HbA_{1c}$ when used in monotherapy as well as when used in combination with other treatments [11, 30, 35–39]. Overall, the reduction in $HbA_{1c}$ is approximately 0.6% to 1.1% depending on the initial baseline $HbA_{1c}$. Furthermore, DPP-4 inhibitors are safe with a low risk for adverse events. The overall incidence of adverse events with DPP-4 inhibitors is not higher than in placebo [42–46]. Furthermore, DPP-4 inhibitors are either weight neutral or slightly reduce body weight, and a consistent finding is that they are associated with low risk for hypoglycemia as monotherapy or when combined with other agents with low risk such as metformin.

### Limitations

Based on published studies lasting up to 2 years and of clinical experience now lasting more than 4 years, there seems to be no limitation to DPP-4 inhibitors in clinical use from a safety and tolerability point of view. A practical limitation is that because clinical experience is low in subjects with renal insufficiency, DPP-4 inhibitors should not be used in this condition unless, for some of the DPP-4 inhibitors, the dose is reduced.

However, an important limitation is that long-term experience, including safety, is lacking. Long-term surveillance is therefore warranted. Also, due to lack of long-term

experience, it is not known whether DPP-4 inhibitors improve complications to type 2 diabetes, including CV risk. Based on surrogate markers, however, this may be likely, because DPP-4 inhibitors have been shown to improve atherogenic markers [47]. However, further studies are required in this area.

## Comparisons Between SUs and DPP-4 Inhibitors as Add-on to Metformin

Five head-to-head studies have compared efficacy, safety, and tolerability of SUs versus DPP-4 inhibitors when added to ongoing metformin therapy in subjects with type 2 diabetes with insufficient glycemic control when treated with metformin alone.

### Glimepiride Versus Vildagliptin

One study examined the efficacy and safety of vildagliptin (50 mg twice daily, $n$=1562) versus glimepiride (up to 6 mg/day, mean dose 4.5 mg/day; $n$=1556) when added to metformin; baseline $HbA_{1c}$ was 7.3%. The results were reported after 1 year [48•] and after completing 2 years [49]. $HbA_{1c}$ was reduced during the initial 24 to 30 weeks in both groups. After 1 year, $HbA_{1c}$ was reduced by 0.44% by vildagliptin and by 0.53% by glimepiride, and after the 2 years, $HbA_{1c}$ was reduced by 0.1% in both groups compared with baseline, showing that vildagliptin and glimepiride are equipotent in reducing glycemia. The study also examined the durability of action of vildagliptin versus glimepiride [49], and found that the increase in $HbA_{1c}$ between week 24 and 104 was significantly lower for vildagliptin (0.4%/year) than for glimepiride (0.5%/year), and by examining sustainability of treatment revealed that patients treated with vildagliptin maintained their initial response for a longer period (309 days) than those treated with glimepiride (244 days). This would suggest a better durability effect by vildagliptin, although it must be emphasized that a 2-year study is too short for allowing conclusions on long-term durability.

There were no differences in the overall number of adverse events between the two groups, with the important exception of hypoglycemia. Hypoglycemia was thus reported in 281 patients (18.2%) treated with glimepiride (838 events), whereas it occurred in 35 patients (2.3%) treated with vildagliptin (59 events). Of particular importance is that severe hypoglycemia occurred in 14 patients treated with glimepiride (8.0%) but only in one patient treated with vildagliptin (0.2%).

Another difference between the two compounds was that whereas vildagliptin was associated with a slight weight loss (0.3 kg), glimepiride treatment resulted in weight gain (+1.2 kg). In regard to dyslipidemia, vildagliptin had a modest beneficial effect compared with glimepiride on high-density lipoprotein cholesterol, total cholesterol, and triglycerides.

In a subgroup of patients, meal tests were undertaken before and after 2 years of treatment; meal-induced glucagon secretion was lowered by vildagliptin, whereas glucagon secretion was increased by glimepiride [42]. This shows that the hyperglucagonemia, which is an important portion of the islet dysfunction in diabetes, was targeted over a 2-years time by vildagliptin but not by glimepiride.

### Glipizide Versus Sitagliptin

Another study evaluated the efficacy and safety of adding sitagliptin (100 mg once daily; $n$=588) versus glipizide (5 mg/day with uptitration to 20 mg/day, mean dose 9.2 mg/day; $n$=584) when added to ongoing metformin; baseline $HbA_{1c}$ was 7.3%. The results were reported after 1 year [43] and after completing 2 years [44]. $HbA_{1c}$ was reduced during the initial 30-week study period in both groups. After the 2 years, baseline $HbA_{1c}$ was reduced by 0.54% by sitagliptin and by 0.51% by glipizide. It was also found that the rise in $HbA_{1c}$ from week 24 to the end of the study was less with sitagliptin (0.16%/year) than with glipizide (0.26%/year). This would suggest a better long-term effect of sitagliptin, although, as underlined above, a study of only 2 years is too short to estimate durability of improved glycemia.

A few specific adverse events were more common in each of the groups but these differences were minor. The only adverse event that showed a large difference between the groups was hypoglycemia. Thus, hypoglycemia was reported in 199 patients (34%) treated with glipizide (805 events), compared with 31 patients (5%) treated with sitagliptin (57 events). Severe hypoglycemia occurred in 18 patients treated with glipizide (7.0%) and in two patients treated with sitagliptin (0.8%).

Also in this study, a difference in body weight was observed between the groups. Thus, sitagliptin was associated with a slight weight loss (−1.6 kg) compared with weight gain (+0.7 kg) with glipizide.

In a subgroup of patients, a meal test was undertaken before and after 2 years with estimation of glucose excursion and β-cell function. It was found that glucose excursion was smaller in the sitagliptin than in the glipizide group. Furthermore, β-cell function (C-peptide data) was stable in the sitagliptin group compared with before the study, whereas a reduction in insulin secretion versus baseline was observed in the glipizide group.

### Gliclazide Versus Vildagliptin

A third study evaluated the efficacy and safety in a 52-week study of adding vildagliptin (50 mg twice daily; $n$=513) versus gliclazide (up to 320 mg/day; $n$=494) to metformin treatment;

baseline $HbA_{1c}$ was 8.5% [45]. After 52 weeks, $HbA_{1c}$ was reduced by 0.81% by vildagliptin and by 0.85% by gliclazide. Six of the patients treated with vildagliptin reported hypoglycemia compared with 11 of the patients on gliclazide. Body weight was not significantly changed by vildagliptin but increased (by 1.4 kg) by glipizide. Apart from hypoglycemia, adverse events were not different between the groups.

### Glipizide Versus Saxagliptin

A fourth study evaluated the efficacy and safety in a 52-week study of adding saxagliptin (5 mg once daily; $n$=588) versus glipizide (5 mg/day with uptitration to 20 mg/day, mean dose 14.7 mg/day; $n$=584) to metformin treatment; baseline $HbA_{1c}$ was 7.7% [46]. After 52 weeks, $HbA_{1c}$ was reduced by 0.74% by saxagliptin and by 0.80% by glipizide. In the patients treated with saxagliptin, 3% reported hypoglycemia, whereas 36% of patients treated with glipizide reported hypoglycemia. Body weight was slightly reduced (by 1.1 kg) by saxagliptin but slightly increased (by 1.0 kg) by glipizide. Apart from hypoglycemia, adverse events were not different between the groups.

### Glimepiride Versus Sitagliptin

A fifth study evaluated the efficacy and safety in a 30-week study of adding sitagliptin (100 mg once daily; $n$=516) versus glimepiride (titration up to 6 mg/day; $n$=519) to metformin treatment; baseline $HbA_{1c}$ was 7.5% [50]. After 30 weeks, $HbA_{1c}$ was reduced by 0.47% by sitagliptin and by 0.54% by glimepiride. A total of 7% of patients treated with sitagliptin reported hypoglycemia (73 events), whereas of those treated with glimepiride, 22% reported hypoglycemia (460 events). Furthermore, body weight was slightly reduced (by 0.8 kg) by sitagliptin but slightly increased (by 1.2 kg) by glimepiride. Apart from hypoglycemia, adverse events were not different between the groups.

These comparative studies show together that DPP-4 inhibition when added to ongoing therapy with metformin in patients with insufficient glycemic control when treated with metformin alone is equipotent with SUs over periods up to 2 years. Furthermore, DPP-4 inhibition is associated with much lower incidence of hypoglycemia than SUs and with a reduction in body weight, whereas SUs increases body weight.

## SUs and DPP-4 Inhibitors as Add-on to Metformin: Which Is Most Desirable?

Several aspects need to be considered when choosing between SUs versus DPP-4 inhibitors as add-on to metformin in patients with insufficient glycemic control when treated with metformin alone:

1. The therapy should target pathophysiologic defects in type 2 diabetes. This is important for being able to prevent deterioration of the disease. This is a great advantage of DPP-4 inhibitors over SUs. Thus, DPP-4 inhibitors a) stimulate insulin secretion, b) inhibit glucagon secretion, both effects being in a glucose-dependent manner, and c) in rodent studies they increase β-cell mass. In contrast, SUs a) stimulate insulin secretion in a glucose-independent manner, b) stimulate rather than inhibit glucagon secretion, and 3) reduce β-cell mass through an augmented apoptosis, as shown in rodents.
2. The treatment should result in clinically meaningful reduction in $HbA_{1c}$. This is undertaken by both DPP-4 inhibitors and SUs because they reduce $HbA_{1c}$ and, in head-to-head studies over 30 weeks to 2 years, they do so in an equipotent manner.
3. The reduction in $HbA_{1c}$ should show sustained durability. Mechanistically, DPP-4 inhibitors have been shown to increase β-cell mass in rodents and GLP-1 reduces rather than increases β-cell apoptosis, which

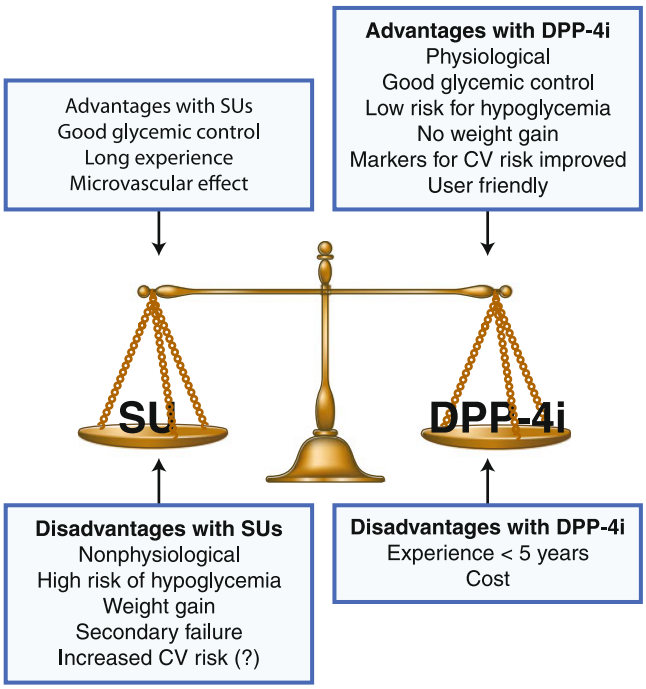


**Fig. 1** Illustration of the balance between advantages and disadvantages for sulfonylureas (SUs) versus dipeptidyl peptidase-4 inhibitors (DPP-4i) in the management of hyperglycemia in 2 diabetes. Management with SU is placed on the left at the balance, whereas management with DPP-4i is placed on the right. Advantages of each of the two approaches are listed above the scale, which make up the force of each strategy to be more desirable over the other, whereas disadvantages are listed below the scale, working against desirability. *CV* cardiovascular

may suggest potential for long-term β-cell preservation and durability. Clinically, DPP-4 inhibitors show durability over the 2 years they have been studied [44, 49]. In contrast, SUs may induce β-cell apoptosis and have in general been associated with poor long-term clinical durability with secondary failures [28]. However, more long-term studies with DPP-4 inhibitors versus SUs are required, and so far no conclusion regarding this criterion is possible.

4. The treatment should be safe with no hypoglycemia, weight gain, or other adverse events. The number of adverse events, apart from hypoglycemia and weight gain, does not seem to differ between SUs and DPP-4 inhibitors in head-to-head studies. However, hypoglycemia, which is rarely observed during treatment with DPP-4 inhibitors, is commonly observed during treatment with SUs, as was clearly demonstrated in the head-to-head studies [42, 44–46, 49, 50]. Similarly, whereas DPP-4 inhibitors are weight neutral or reduce body weight, there is an increase in body weight during treatment with SUs.
5. The treatment should prevent retinopathy, nephropathy, and neuropathy, and reduce the risk for CV events. SUs have been shown to prevent microangiopathic complications to diabetes [1], whereas no such evidence exists for the DPP-4 inhibitors. In regard to reducing CV risk, no clear evidence for such an effect of SUs exist [20]. For DPP-4 inhibitors, no long-term studies with hard end-point data have been performed; such studies are under way.
6. The treatment should be acceptable for the patient, the health care providers, and the community, including a favorable cost-benefit profile. There is a difference in how the treatment is initiated, in that SUs need uptitration, whereas DPP-4 inhibitors are given at the same dose in all patients, except in those with renal impairment. This may indicate that DPP-4 inhibitors are more user friendly, to which is added that self glucose monitoring is not required in patients treated with DPP-4 inhibitors, due to the low risk for hypoglycemia. Another advantage for DPP-4 inhibitors is that patients given these compounds do not need to fear hypoglycemia or increased body weight, which are limitations to SUs. On the contrary, pricing is an advantage for SUs because these are cheaper. However, in this context it needs to be emphasized that a full health economy analysis needs to be undertaken including additional costs due to hypoglycemic events and long-term failure.

## Conclusions

The development and introduction of SUs in the treatment of type 2 diabetes had a tremendous importance for the patients because they were offered efficient oral treatment to combat the disease. SUs have also been in the center of treatment for several decades. However, after more than 50 years of use, researchers have provided the patients and clinicians with a class of compounds that may challenge the SUs as central compounds for management of hyperglycemia in type 2 diabetes. As is evident from this article, several different aspects can be raised when comparing the two groups. Figure 1 illustrates the different aspects.

It is clear from the comparisons reported here and illustrated in Fig. 1 that there are several advantages of DPP-4 inhibitors over SUs. Thus, the important limitations with SUs (ie, the high risk for hypoglycemia and the increase in body weight) are not seen with DPP-4 inhibitors. Furthermore, in terms of efficacy, the two approaches seem equipotent over the 2-year periods they have been compared, but based on animal studies, DPP-4 inhibitors might be more favorable in terms of potential for long-term durability. However, it is very important with long-term surveillance to explore the long-term safety of DPP-4 inhibitors, and, also, to establish the long-term consequences for secondary complications to diabetes. SUs have a good record for microvascular complications, but less convincing for macrovascular complications. Any long-term benefits of any treatment of type 2 diabetes will be more important than the cost of the compound; the price issue may therefore become less important as times go by. The conclusion of the comparison between SUs and DPP-4 inhibitors is that SUs have been the number one agent to add-on to metformin for many decades, but now they are less desirable than the new DPP-4 inhibitors, although long-term efficacy and safety (>4 years) are still needed for DPP-4 inhibitors.

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