Glucose effectiveness: Lessons from studies on insulin-independent glucose clearance in mice

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INTRODUCTION
A major mechanism for glucose disappearance from the circulation is insulin-mediated transport into the cells. However, as shown >80 years ago, there is also a non-insulin-dependent process that is mediated by glucose itself to enhance its uptake and metabolism. This was confirmed >40 years ago, when the minimal modeling of glucose and insulin data from an intravenous glucose tolerance test (IVGTT) showed that non-insulin-mediated processes play a major role in glucose disappearance; these processes were described by the term "glucose effectiveness"². The aim of the present review was to elucidate the relevance of glucose effectiveness for glucose disappearance under various physiological and pathophysiological conditions. Understanding the regulation of glucose effectiveness might also have potential therapeutic benefits for glucose-lowering attempts in type 2 diabetes. We have therefore reviewed the clinical studies reporting glucose effectiveness as estimated from IVGTT, and we have also retrospectively analyzed changes of glucose effectiveness in multiple different conditions in mice, where a series of IVGTTs have been carried out under standardized conditions.

HISTORY AND DEFINITION
The history of glucose effectiveness goes back to the late 1970s, when Bergman et al.³ formulated the equation system of the minimal model to describe glucose disappearance during an intravenous glucose administration in dogs. They then found that it was not possible to describe glucose disappearance only with the contribution of insulin⁴. Instead, a parameter describing the insulin-independent mechanism was necessarily introduced. This parameter was termed "glucose effectiveness" (p₁), although no specific discussion on p₁ appeared in this first paper, which was focused on insulin sensitivity (S₁). The existence of a non-insulin-dependent glucose disposal was also shown in the first study in humans with the minimal model, where again the parameter p₁ was termed "glucose effectiveness"³. Similarly, in a study of glucose uptake in the absence of a sustained insulin response, it was observed that hyperglycemia increases glucose uptake, further suggesting an insulin-independent glucose-dependent glucose uptake in humans⁴.

Glucose effectiveness is today referred to as the ability of glucose per se to suppress endogenous glucose production and stimulate peripheral glucose uptake, as was elegantly shown in dogs by Ader et al.⁵ The acronym for glucose effectiveness that we use today (S₂) was first used in a human study in 1985,
where it was stated that “SG (formerly p1) [is] the insulin-independent fractional glucose disappearance”66. In the classic review by Bergman et al.7 of the same year that canonized the minimal model approach as a reliable method to assess insulin sensitivity, parameter p1 was still used in the equations, but it was stated that p1 is SG, defined as a “measure of the effect of glucose to enhance its own disappearance [within the extracellular glucose pool] at basal insulin, independent of any increase in insulin”. In subsequent years, papers exploring the minimal model have also reported glucose effectiveness, either as p18,9 or as SG10,12, or only mentioned SG without discussing p115. Glucose effectiveness has also been estimated with combined eu- and hyperglycemic clamp14, with similar conclusions as achieved by the minimal modeling approach, as recently was reviewed15.

**GLUCOSE EFFECTIVENESS AND CLINICAL CONDITIONS**

As glucose effectiveness is the “ability of glucose per se without any change in insulin to disappear from blood”5,16, it quantifies the fractional rate (min⁻¹) of glucose utilization in the brain, central nervous system, red blood cells and other insulin-independent tissues/organs, such as kidneys. Renal excretion of glucose, which is an insulin-independent process, also contributes to SG. Glucose effectiveness is calculated from a minimal model of insulin and glucose data after an IVGTT17-18. The model assumes a first-order non-linear insulin-controlled kinetic, and accounts for the effect of insulin and glucose itself on glucose disappearance after exogenous glucose injection. The model provides two parameters: S₀, which is defined as the ability of insulin to enhance glucose disappearance and inhibit glucose production (i.e., insulin sensitivity), and SG, representing glucose disappearance from plasma without any change in dynamic insulin3,17,18. The mathematical procedure for minimal model parameters (thus SG) is explained in detail previous studies17,18, which show how SG is estimated through a series of mathematical steps when the model differential equations are applied to a set of IVGTT data.

Several early studies documented the large contribution of this insulin-independent glucose disposal to overall glucose disposal in humans19,20, which was continuously appreciated21,22, even recently15,23. Several studies also examined SG in various clinical conditions. Table 1 summarizes many of these studies. Studies have thus shown that SG is reduced in obesity24, type 2 diabetes25,26, gestational diabetes27, liver cirrhosis28 and USA older adults29,30, whereas SG is increased in growth hormone deficiency31 and after administration of glucagon-like peptide-1 (GLP-1)32-34. In contrast, SG is not changed in impaired glucose tolerance30 or by treatment with thiazolidinediones35; the GLP-1 receptor agonist, liraglutide36; or the dipeptidyl peptidase-4 (DPP-4) inhibitor, vildagliptin37, in type 2 diabetes patients; or after carbohydrate dieting in USA older adults31 or in Italian older adults with a normal oral glucose test12. These studies have been undertaken mainly in white people, but the result that SG is reduced in type 2 diabetes has also been reported in Malaysian38, Japanese39 and Chinese people40, whereas in contrast, similar SG in type 2 diabetes patients as controls has been reported in African Americans41 and Ghanaians42. Therefore, different ethnic groups might show differences in the impact on type 2 diabetes by SG. However, in impaired glucose tolerance, SG was found to be lower than in controls in Japanese people43, but not reduced in white people29 or in African Americans44. These differences are of interest on the background that type 2 diabetes in Asian people is primarily characterized by impaired insulin secretion rather than an interplay between insulin resistance and failed islet compensation44. The finding of reduced SG in individuals with impaired glucose tolerance among Japanese individuals43 would suggest that reduced glucose effectiveness contributes to diabetes development in these patients, and this is supported by the results of a study showing reduced SG in the offspring of Japanese patients with type 2 diabetes even at normal glucose tolerance62. However, to study whether the contribution by SG to the development of type 2 diabetes is different in ethnic groups, direct comparisons need to be carried out in individual studies. One such study has compared SG in two different ethnic groups (Mexican Americans and non-Hispanic white Americans) showing no difference46. However, more studies are required for examining SG in other ethnic groups.

**APPROACH TO STUDY GLUCOSE EFFECTIVENESS IN MICE**

To study the physiological and pathophysiological meaning of glucose effectiveness and its mechanism of action, in the 1990s we adapted the minimal model to standardized mouse experiments18,47. This allowed more detailed studies on physiology and regulation of SG, and the knowledge of SG has therefore been expanded during the past decades. When translated for studies that use the minimal model in mice, the following protocol has been used: after a 5–h fast during the late morning hours, mice (most often from the NMRI or C57BL/6j strain) are anesthetized with an intraperitoneal injection of a fixed-dose combination of fentanyl (0.02 mg/mouse)–fluanisone (0.5 mg/mouse) and midazolam (0.125 mg/ mouse). After 30 min, a blood sample (40 µL) is taken from the retroorbular, intraorbital sinus capillary plexus in pipette tubes that have been pre-rinsed in heparin solution (100 U/mL in 0.9% NaCl). Thereafter, mice are given an intravenous bolus dose of glucose (dissolved in saline) over a period of 3 s in a tail vein, and whole blood is sampled as aforementioned at 1, 5, 10, 20, 30 and 50 min after glucose injection. Glucose is detected in whole blood, and plasma is immediately separated after collection and stored at −20°C until analysis for insulin. Regarding the possible influence on the estimation of SG during IVGTT of the renal glucose excretion, it is worth noting that the peak glucose levels after the injection could be above the kidney glucose threshold. However, although it is known that the renal glucose threshold for mice is ≈22 mmol/L48, such high values are rarely seen after the standard glucose injection or are observed for only a very short period of time after the glucose
### Table 1 | Glucose effectiveness in various clinical studies

| Studies                  | Comparisons                      | \( S_G \) (No. participants) | Reference |
|--------------------------|----------------------------------|-------------------------------|-----------|
| Obesity                  | Lean Obese                       | 0.030 ± 0.003 (18)           | 24        |
| Type 2 diabetes          | Type 2 diabetes Controls         | 0.014 ± 0.002                | 25        |
| Type 2 diabetes          | Type 2 diabetes Controls         | 0.024 ± 0.003*               | 26        |
| Gestational diabetes     | GDM NGT                          | 0.022 ± 0.002                | 27        |
| Cirrhosis                | Cirrhosis Controls               | 0.024 ± 0.003 (6)            | 28        |
| Aging                    | Mean 65 years Young men (18–36 years) Elderly men (65–82 years) | 0.029 ± 0.005 (8) | 29        |
| GH administration in GH deficiency | GH deficiency Controls | 0.010 ± 0.001 (8)* | 30        |
| GLP-1 administration in healthy individuals | Controls | 0.018 ± 0.001 (6) | 31        |
| GLP-1 administration in healthy individuals | GLP-1 | 0.026 ± 0.003 (6) | 32        |
| GLP-1 administration in healthy individuals | Controls | 0.018 ± 0.002 (17) | 33        |
| GLP-1 administration in healthy individuals | GLP-1 | 0.025 ± 0.002 (17) | 34        |
| Women with IGT           | NGT                              | 0.019 ± 0.003 (10)           | 35        |
| Treatment with TZD of women at high risk for type 2 diabetes | Women with recent GDM and IGT After 12 weeks TZD treatment | 0.014 ± 0.003 (14) | 36        |
| Treatment with liraglutide in type 2 diabetes | Placebo | Change 0.0008 (--0.003, 0.006) | 37        |
| Treatment with vildagliptin in type 2 diabetes | Placebo | Vildagliptin | 0.019 ± 0.002 (14) | 38        |
| Carbohydrate diet        | Young men (18–36 years) Elderly men (65–82 years) | 0.029 ± 0.005 (8) | 39        |
| Type 2 diabetes in Malaysians | Type 2 diabetes Controls | 0.012 ± 0.005                | 40        |
| Type 2 diabetes in Japanese people | Type 2 diabetes Controls (offspring) | 0.011 ± 0.003 (9) | 41        |
| Type 2 diabetes in Chinese people | Insulin sensitive type 2 diabetes | 0.013 ± 0.008 (71) | 42        |
| Type 2 diabetes and IGT in African Americans | NGT | 0.029 ± 0.002 (101) | 43        |
| Type 2 diabetes in Ghanaians | Type 2 diabetes Controls | 0.025 ± 0.001*               | 44        |
| IGT in Japanese people   | NGT                              | 0.025 ± 0.002 (15)           | 45        |
| Offspring to Japanese patients with type 2 diabetes | Offspring | 0.016 ± 0.002 (9)* | 46        |
| Ethnic groups            | Mexican Americans Non-Hispanic whites | 0.022 ± 0.002 (10) | 47        |

Values are the mean ± standard error or median (95% confidence intervals). *Significant differences between the groups (\( P < 0.05 \)). GDM, gestational diabetes mellitus; GH, growth hormone; GLP-1, glucagon-like peptide-1; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; TZD, thiazolidinedione.
challenge, and therefore, it is likely that the contribution of this process to $S_G$ is negligible.

With this technique, $S_G$ has been shown to be approximately $0.050 \text{ min}^{-1}$ in normal mice, with a standard error of the mean of $0.006^{47}$. This is equivalent to a glucose disposal of 5% of the extracellular glucose pool per min by glucose-dependent insulin-independent mechanisms. This value is higher than the $0.021 \text{ min}^{-1}$ reported in humans$^{22}$ and $0.028 \text{ min}^{-1}$ in dogs$^{5}$, but comparable to the reported values in rats, which range from $\approx 0.040 \text{ min}^{-1}$ in obese Zucker rats to $\approx 0.053 \text{ min}^{-1}$ in lean Zucker rats$^{49}$, and $\approx 0.070 \text{ min}^{-1}$ in Long-Evans rats$^{50}$ and $\approx 0.090 \text{ min}^{-1}$ in endurance-trained animals$^{51}$. Furthermore, several studies have been carried out to understand the factors that might regulate $S_G$ in mice, as it is summarized in Table 2. The incretin hormones, GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), as well as exogenous administration of insulin, increase $S_G$; whereas $S_G$ is not significantly affected by the neuuropeptide, pituitary adenylate cyclase activating polypeptide, or in gastrin-releasing peptide knockout mice, and reduced by glucagon, in GLP-1 receptor knockout mice, in high-fat fed and insulin-resistant mice, as well as after inhibition of insulin secretion$^{47,52-57}$. These data thus show that $S_G$ is a process exposed to a complex regulation, and suggest that $S_G$ might contribute to changes in glucose tolerance under a number of different conditions.

### CONTRIBUTION BY GLUCOSE EFFECTIVENESS TO GLUCOSE DISAPPEARANCE

The importance of $S_G$ on glucose tolerance was proposed in a study by Best et al.$^{39}$ from analyzing the linear regression between intravenous glucose elimination rate, $K_G$, and $S_G$. That study showed that insulin-independent glucose uptake contributes by $\approx 72\%$ to glucose disappearance, indicating that it is the major determinant of intravenous glucose tolerance. This evidence confirmed what was previously shown in dogs$^{5}$, where it emerged that $S_G$ contributes by $70\%$–$80\%$ to glucose disappearance, later further corroborated by Ader et al.$^{16}$.

In normal mice, we reached a similar conclusion of a large contribution by glucose effectiveness to glucose disposal with a complex study exploiting IVGTT and glucose clamp$^{47}$. We used sensitivity analysis, which provides estimates of changes of a dependent variable ($K_G$) for a unit change of independent variables, and accurately describes in quantitative terms the relationships among those variables$^{47,58}$. Some requirements, however, had to be fulfilled for a correct use of this method. First, we showed that $S_G$ is independent from both insulin and $S_I$ in the model. Also, we considered that the total contribution to the net glucose disappearance was ascribed to $S_G$ when insulin did not change. With these assumptions, we showed that insulin (through secretion and effect) contributes to glucose tolerance by $29\%$–$6\%$ in normal conditions (Figure 1). Therefore,

### Table 2 | Glucose effectiveness in mouse experiments

| Studies                        | Comparisons                        | $S_G$ (No. animals) | Reference |
|--------------------------------|------------------------------------|---------------------|-----------|
| GIP receptor knockout          | GIP receptor knockout              | $0.061 \pm 0.004$ (26) | $^{52}$   |
|                                | Controls                           | $0.057 \pm 0.005$ (30) |           |
| GLP-1 receptor knockout        | GLP-1 receptor knockout            | $0.027 \pm 0.004$ (17)* | $^{52}$   |
|                                | Controls                           | $0.044 \pm 0.005$ (17) |           |
| Incretin hormones              | GIP                               | $0.072 \pm 0.004$ (40)* | $^{53}$   |
|                                | GLP-1                             | $0.066 \pm 0.005$ (47)* |           |
|                                | Controls                           | $0.045 \pm 0.003$ (106) |           |
| GRP receptor knockout          | GRP receptor knockout              | $0.052 \pm 0.007$ (50) | $^{54}$   |
|                                | Controls                           | $0.038 \pm 0.004$ (50) |           |
| High-fat feeding               | High-fat feeding for 10 months     | $0.030 \pm 0.004$ (24)* | $^{55}$   |
|                                | Controls                           | $0.056 \pm 0.006$ (23) |           |
| Effect of insulin              | Insulin administration             | $0.075 \pm 0.004$ (48)* | $^{47}$   |
|                                | Blocking of insulin secretion      | $0.014 \pm 0.002$ (24)* |           |
|                                | Controls                           | $0.050 \pm 0.002$ (202) |           |
| PACAP-27                       | PACAP-27                           | $0.041 \pm 0.005$ (16) | $^{56}$   |
|                                | Controls                           | $0.040 \pm 0.006$ (16) |           |
| PACAP-38                       | PACAP-38                           | $0.057 \pm 0.008$ (24) | $^{56}$   |
|                                | Controls                           | $0.043 \pm 0.006$ (24) |           |
| Glucagon                       | Glucagon (10 nmol/kg)              | $0.038 \pm 0.004$ (24) | $^{57}$   |
|                                | Controls                           | $0.058 \pm 0.005$ (135) |           |
| GLP-1                          | GLP-1 (3.0 nmol/kg)                | $0.066 \pm 0.005$ (47)* | $^{53}$   |
|                                | Controls                           | $0.045 \pm 0.003$ (106) |           |
| GIP                            | GIP (3.0 nmol/kg)                  | $0.072 \pm 0.004$ (40)* | $^{53}$   |
|                                | Controls                           | $0.045 \pm 0.003$ (106) |           |

*Significant differences between the groups ($P < 0.05$). GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; GRP, gastrin releasing peptide; PACAP, pituitary adenylate cyclase activating polypeptide.
we confirmed that insulin-independent mechanisms; that is, $S_G$, contributes by more than two-thirds to glucose disappearance.

We also studied $S_G$ when insulin secretion had been completely blocked and therefore no change in dynamic insulin is possible. This was achieved by the drug, diazoxide, which completely inhibits insulin secretion through a direct effect on the $\beta$-cells; in mice, it was not possible to use somatostatin, as it never completely inhibited insulin secretion. Diazoxide was administered subcutaneously to mice at the dose of 25 mg/kg 10 min before the intravenous administration of glucose. This resulted in complete inhibition of insulin secretion, but yet an efficient glucose disappearance persisted. Figure 1 shows the results. It is seen that glucose disposal was impaired, but not absent, during diazoxide (in red), although the insulin response was totally inhibited (Figure 1b). Diazoxide was administered subcutaneously to mice at the dose of 25 mg/kg 10 min before the intravenous administration of glucose. This resulted in complete inhibition of insulin secretion, but yet an efficient glucose disappearance persisted. Figure 1 shows the results. It is seen that glucose disposal was impaired, but not absent, during diazoxide (in red), although the insulin response was totally inhibited (Figure 1b).

**RELATIONSHIP BETWEEN GLUCOSE EFFECTIVENESS AND INSULIN**

$S_G$ is estimated as the insulin-independent glucose disposal, and should therefore be independent from insulin. However, under certain conditions, there is a relationship between $S_G$ and the insulin secretory function. We verified this by showing that $S_G$ is reduced when insulin secretion is blocked by diazoxide.

This could suggest either that $S_G$ is overestimated by the minimal model (as $S_G$ during diazoxide should theoretically estimate the “true” $S_G$) or that $S_G$ also requires insulin, even though its dynamics are not dependent on changes in insulin. However, when correlating $S_G$ with the area under the insulin curves ($AUC_{\text{insulin}}$) in studies with a wide span of insulin concentrations, no correlation was observed, except for extremely elevated values of peak insulin when $S_G$ was reduced, perhaps as a protection against hypoglycemia. These results suggest that basal insulin and $S_G$ synergistically cooperate such that an increase in insulin during IVGTT is required for $S_G$ and, furthermore, that at extremely high insulin levels, $S_G$ is reduced.

**RELATIONSHIP BETWEEN GLUCOSE EFFECTIVENESS AND GLUCOSE**

To evaluate whether the estimation of $S_G$ is affected by the prevailing glycemia, we collected a series of IVGTT experiments carried out in 83 normal mice (glucose dose 0.35 g/kg). The total $AUC_{\text{glucose}}$ ranged from 380 to 880 mol/L-min in 50 min (averaging 555 ± 11 mol/L-min), and the mean peak (1 min) value of glucose was 17 ± 0.3 mmol/L. The mean $S_G$ was 0.045 ± 0.003 min⁻¹, and did not correlate with either $AUC_{\text{glucose}}$ ($R^2 = 0.0003; P > 0.5$) or the peak glucose ($R^2 = 10^{-3}; P > 0.1$). This shows that the estimation of $S_G$ is independent of glucose levels reached during the tests. This is also evident from a novel ad hoc series of experiments with IVGTT with two different doses of glucose in mice. Mice were anesthetized as explained above, and injected intravenously with glucose at either 0.35 g/kg (low dose; n = 17) or at 0.75 g/kg.
(high dose; \( n = 16 \)), which yield extremely different glucose levels; samples were taken with the usual protocol, and \( S_G \) estimated from glucose and insulin data. The results are reported in Figure 2. It is evident that the estimation of \( S_G \) is independent of the glucose levels reached during the test: \( S_G \) was 0.053 ± 0.003 min\(^{-1}\) at the glucose dose of 0.35 g/kg, and 0.057 ± 0.004 min\(^{-1}\) at 0.75 g/kg (not significantly different; \( P = 0.47 \)). Hence, levels of circulating glucose do not affect the assessment of \( S_G \).

**RELATIONSHIP BETWEEN GLUCOSE EFFECTIVENESS AND INSULIN RESISTANCE**

Elevated insulin is a characteristic of insulin resistance. In humans, insulin resistance in obesity\(^{24}\), liver cirrhosis\(^{28}\) and pregnancy with or without gestational diabetes\(^{27}\) are associated with a 30–50% reduction in \( S_G \). Therefore, it has been of interest to deeply evaluate the role of \( S_G \) in insulin resistance; that is, if either \( S_G \) follows the pattern of insulin sensitivity or is increased in insulin resistance to augment glucose uptake. To study this, we used mice given a high-fat diet for 10 months\(^{55}\). In this model, bodyweight is increased, along with a reduction in insulin sensitivity and an adaptive increase in insulin secretion; nevertheless, glucose disposal is reduced\(^{60}\). We carried out IVGTT at 1 week, and 1, 3 and 10 months after initiation of a high-fat diet\(^{55}\). As expected, we found that bodyweight increased, \( S_I \) was markedly reduced and insulin levels were compensatorily increased. Figure 3 shows the \( S_G \) in these experiments. It is seen that \( S_G \) was reduced by high-fat feeding, and this effect was already evident after 1 week. The contribution of \( S_G \) to glucose disappearance was reduced to approximately 40% at this time point. Interestingly, \( S_G \) slightly improved after the first week of high-fat feeding, although it was always lower than in mice fed a control diet. This was at variance with insulin sensitivity, which progressively deteriorated over time in mice fed a high-fat diet. Increased \( S_G \) over time in insulin resistance might therefore be a counterbalance of the elevated insulin resistance, but the main conclusion of this study is that insulin resistance is also associated with a reduced \( S_G \), which therefore might add to the glucose intolerance in this condition.

**GLUCOSE EFFECTIVENESS AND INCRETIN HORMONES**

GLP-1 and GIP are known to stimulate insulin secretion, and therefore enhance insulin levels\(^{61}\). This is a major effect behind the development of GLP-1 receptor agonists\(^{62}\) and DPP-4 inhibitors\(^{63}\) as glucose-lowering therapy for type 2 diabetes. We carried out a study on the effects of GIP versus GLP-1 in C57BL/6J mice\(^{53}\). We found that both incretin hormones augmented glucose-stimulated insulin secretion in a dose-dependent manner\(^{53}\). We found that both incretin hormones also increased \( S_G \)\(^{53}\). Here, we have revisited those data and explored the \( S_G \) results in relation to various administered dose of incretin hormone. Interestingly, as seen in Figure 4, GIP was more potent that GLP-1 in augmenting \( S_G \), as a clear effect was observed by the dose of 0.03 nmol/kg, whereas the lowest effective dose of GLP-1 was 10-fold higher. In contrast, an earlier study in NMRI mice showed only modest changes in \( S_G \) by

![Graph](image-url)
increasing GLP-1 doses\textsuperscript{64}. In humans, it was also shown that GLP-1 augments $S_G$\textsuperscript{32-34}. This suggests that increased $S_G$, together with the classical incretin effect to stimulate insulin secretion, might be a mechanism to prevent hyperglycemia. This would also be supported by a finding that glucose effectiveness is increased during the early phase of an oral glucose tolerance test when the incretin effect is at its zenith\textsuperscript{65}. We have also shown that $S_G$ is reduced in GLP-1 receptor knockout mice, which further shows the impact of GLP-1 on insulin-independent glucose disappearance\textsuperscript{52}. In contrast, $S_G$ is not significantly altered in GIP receptor knockout mice\textsuperscript{52}.

As incretin hormones increase circulating insulin after intravenous glucose, it is still not established whether the increase by GIP and GLP-1 of $S_G$ is due either to the increasing insulin, regardless of the stimulus, or to a primary effect of incretins themselves. Evidence from other studies seem to support the first hypothesis, as other potent enhancers of glucose-stimulated insulin secretion also similarly increase $S_G$ in mice, such as the neuropeptide, pituitary adenylate cyclase activating polypeptide\textsuperscript{47,56}. However, as previously discussed, high insulin levels, if anything, reduce $S_G$; thus, it is more likely that incretin hormones enhance $S_G$ through an extrapancreatic effect independently from their stimulation of insulin secretion. In support of this, we consider again the lack of association between $S_G$ and AUC\textsubscript{insulin} after GLP-1 and GIP\textsuperscript{53}. Such an effect would be consistent with extrapancreatic actions of GIP\textsuperscript{66,67}; also, GLP-1 has been shown to have extrapancreatic effects that might directly (through the liver) or indirectly (through neural effects) affect glucose disposal\textsuperscript{68-71}.

An interesting consequence of the finding of enhanced $S_G$ by incretin hormones is that the proportion of the relative contribution of insulin-dependent and non-insulin-dependent mechanisms to glucose disposal is increased, which was significant for GIP. Thus, a GIP-induced increase in glucose disappearance was associated with a higher dependency on $S_G$ than after glucose alone and after glucose plus GLP-1\textsuperscript{53}. This suggests that GIP enhances the processes driving non-insulin-dependent glucose clearance, which, again, would fit with extrapancreatic actions of GIP.

GLP-1 receptor agonists and DPP-4 inhibitors are frequently used as antihyperglycemic therapy in type 2 diabetes patients\textsuperscript{61,63}. Both these therapies work through GLP-1 receptors, the GLP-1 receptor agonists by achieving a pharmacological activation of the receptors, and DPP-4 inhibitors by preventing the inactivation of endogenously produced GLP-1, thereby increasing the GLP-1 receptor activation by endogenous GLP-1. It is therefore of interest to discuss whether the improved $S_G$ observed when GLP-1 is administered to healthy volunteers\textsuperscript{32-34} might contribute to the metabolic benefits of these therapies. One study explored this by comparing $S_G$ after 12 weeks of treatment with the GLP-1 receptor agonist liraglutide in combination with metformin versus metformin alone in type 2 diabetes for 12 weeks using a cross-over design\textsuperscript{36}, and another study explored the effect of the DPP-4 inhibitor, vildagliptin, versus a placebo during 10 days of treatment in type 2 diabetes patients\textsuperscript{17}. It was found, however, that neither liraglutide nor vildagliptin did increase $S_G$ in these studies\textsuperscript{36,37}. This would therefore suggest that although GLP-1 is able to increase $S_G$ in

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**Figure 3** | Glucose effectiveness ($S_G$) in mice fed a control diet (11% fat; $n = 23$) or a high-fat diet (58% fat, $n = 24$) for up to 10 months. The mean ± standard error of the mean is shown. Data from experiments reported by Ahrén et al.\textsuperscript{55} Asterisks indicate probability level of random difference between the groups, *$P < 0.05$, **$P < 0.01$.

**Figure 4** | Glucose effectiveness ($S_G$) after intravenous administration of glucose-dependent insulinotropic polypeptide (GIP) or glucagon-like peptide-1 (GLP-1) at different dose levels in an intravenous glucose tolerance test in C57BL/6j mice. The mean ± standard error of the mean is shown. There were 83 mice in the glucose-only group (dose 0), and a total of 152 animals in the GLP-1/GIP supplemented groups. Revisited data from results reported by Pacini et al.\textsuperscript{53}.
healthy individuals, therapy with GLP-1 receptor agonists or DPP-4 inhibitors does not seem to increase the low $S_G$ associated with type 2 diabetes. This could be explained by the reduced $S_G$ in type 2 diabetes, which might be more difficult to increase than in healthy individuals, but it might also be due to a failure of GLP-1 to continuously increase $S_G$ over a long period of time. Further studies are required to solve whether GLP-1 receptor agonists and DPP-4 inhibitors affect $S_G$ during prolonged treatment of type 2 diabetes.

**GLUCOSE EFFECTIVENESS AND GLUCAGON**

The decrease of glucose concentration during the IVGTT after the peak caused by the bolus glucose injection is mainly due to glucose uptake and inhibition of glucose production. It is known that glucagon is strictly related to endogenous (liver) glucose production; therefore, studying the effects of glucagon on $S_G$ could provide information on the probable actions that this pancreatic hormone exerts on glucose effectiveness and, consequently, hypothesize possible relationships between $S_G$ and glucose production.

To this aim, glucagon at different doses was added to the glucose bolus\(^{57}\). The results show (Table 1) that supplementing glucagon to glucose reduces $S_G$ by approximately 30% on average\(^{57}\). This indicates that glucagon diminishes glucose effectiveness, suggesting that $S_G$ reflects glucose production during hyperglycemia. As GLP-1 increases $S_G$, we carried out a series of experiments in mice where GLP-1 was added to glucagon. This addition, however, did not modify $S_G$ compared with glucagon alone, indicating that GLP-1 does not increase $S_G$ under conditions when glucagon levels are elevated. We conclude that glucagon is more potent as an inhibitor of $S_G$ than GLP-1 as an enhancer.

**POSSIBLE MECHANISMS OF GLUCOSE EFFECTIVENESS**

Glucose per se is a fundamental substrate for liver metabolism\(^{22}\), and understanding the mechanisms of its regulation is paramount. Glucose effectiveness plays an essential role in this regulation; however, the molecular mechanisms underlying glucose effectiveness are not well defined yet. A study in individuals with hepatic cirrhosis showed that $S_G$ is reduced by 38%, which explained 65% of the glucose intolerance in these individuals\(^{28}\). This would be consistent with a hypothesis that $S_G$ is exerted in the liver, where $S_G$ would be linked to the stimulation of glucose uptake. However, as liver cells do not have the capacity to take up glucose, and there is no correlation between $S_G$ and liver enzymes in cirrhotic patients\(^{28}\), it is more likely that the reduction of $S_G$ in cirrhotic patients is a result of a reduced muscle mass, suggesting that $S_G$ is primarily exerted in the muscles\(^{23}\). Glucose transporters might be candidates for new studies; for instance, it is known that the glucose transporter 4 causes entry of glucose into muscular cells after its translocation to the membrane\(^{24}\). However, as the molecular bases for $S_G$ are still largely unknown, further studies on these topics are required.

**RELEVANCE OF MONITORING INSULIN-INDEPENDENT GLUCOSE DISPOSAL**

As already seen, $S_G$ has been evaluated in several clinical conditions (Table 1), where it has been shown to vary, making it a relevant factor for the assessment of glucose tolerance and turnover of an individual. It is worth noting that the recent availability of sodium–glucose cotransporter 2 inhibitors as antidiabetic agents has offered a therapeutic approach acting directly on the kidneys without requiring insulin action\(^{75,76}\). In line with this, sodium–glucose cotransporter 2 inhibition has been shown to improve the reduced glucose effectiveness in the liver in diabetic Zucker fatty rats\(^{77}\). For this reason, glucose effectiveness might become a fundamental parameter for the evaluation of the influence of such compounds on glucose disposal. When the molecular mechanisms underlying $S_G$ are more established, there will also be a potential to target these mechanisms to increase $S_G$ in glucose-lowering therapy of type 2 diabetes patients.

**CONCLUSIONS**

Glucose effectiveness describes the processes of insulin-independent mechanisms of glucose disposal. It is estimated by modeling glucose and insulin data after an intravenous glucose administration, and it accounts for \(\approx 70\%\) of glucose disposal. It is reduced in type 2 diabetes\(^9\) and obesity\(^{24,78}\), and experimental model studies in mice have characterized the regulation of glucose effectiveness with special emphases on the role of glucose, insulin, and processes stimulating insulin secretion. It is essential, therefore, to evaluate this parameter any time a metabolic test is carried out, especially in large population studies\(^{79}\). Further studies are warranted to explore the regulation of glucose effectiveness, its molecular basis and the potential of targeting glucose effectiveness as a glucose-lowering approach in type 2 diabetes patients.

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**DISCLOSURE**

The authors declare no conflict of interest.

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