Hepatic Dysfunction and Insulin Insensitivity in Type 2

Diabetes Mellitus: A Critical Target for Insulin-Sensitizing Agents

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Abstract

The liver plays an essential role in maintaining glucose homeostasis, including by insulin-mediated processes such as hepatic glucose output and uptake, as well in clearance of insulin itself. In Type 2 diabetes, the onset of hyperglycemia (itself a potent inhibitor of hepatic glucose output), alongside hyperinsulinemia, indicates the presence of hepatic insulin insensitivity. Increased hepatic glucose output is central to the onset of hyperglycemia, and highlights the need to target hepatic insulin insensitivity as a central component of antihyperglycemic therapy. The mechanisms underlying the development of hepatic insulin insensitivity are not well understood, but may be influenced by factors such as fatty acid oversupply and altered adipocytokine release from dysfunctional adipose tissue and increased liver fat content. Furthermore, although the impact of insulin insensitivity as a marker of cardiovascular disease is well known, the specific role of hepatic insulin insensitivity is less clear. The pharmacological tools available to improve insulin sensitivity include the biguanides (metformin) and thiazolidinediones (rosiglitazone and pioglitazone). Data from a number of sources indicate that thiazolidinediones in particular can improve multiple aspects of hepatic dysfunction, including reducing hepatic glucose output, insulin insensitivity and liver fat content, as well as improving other markers of liver function and the levels of mediators with potential involvement in hepatic function, including fatty acids and adipocytokines. The current review addresses this topic from the perspective of the role of the liver in maintaining glucose homeostasis, its key involvement in the pathogenesis of Type 2 diabetes, and the tools currently available to reduce hepatic insulin insensitivity.
Introduction

Type 2 diabetes is defined and diagnosed on the basis of hyperglycemia, although the extent of the metabolic dysfunction is much broader than glucose metabolism. Hyperglycemia is often conceived as resulting from a combination of impaired insulin action (reduced insulin sensitivity or ‘insulin resistance’) and a progressive loss of islet β-cell responsiveness [1]. However, glucose metabolism can be characterized as being abnormal in other ways, such as decreased glucose-mediated glucose disposal and loss of hepatic autoregulation of glucose concentrations [2, 3], suggesting more fundamental defects of liver and muscle metabolism may underlie what is loosely described as insulin insensitivity. A notable third contributor to hyperglycemia is glucose toxicity, exacerbating the defects defined above and thus magnifying any tendency to raised blood glucose levels [2–4]. While these abnormalities of tissue glucose metabolism are usually descriptively characterized as insulin insensitivity and glucose insensitivity, the more fundamental property of substrate flux (i.e. glucose mass action) will also contribute to determining the rate of glucose disposal in peripheral tissues [3].

At steady-state glucose concentrations, glucose uptake peripherally must equal glucose input into the circulation (from liver, gut and kidney). If hepatic glucose output is abnormally high, glucose concentration in the blood will rise to the point at which concentration-driven glucose disposal compensates for the increased glucose input into the blood (which would occur even in the absence of insulin sensitive tissues). This situation may be complicated by down regulation of glucose transporters in metabolically active tissues such as the brain [5], which will decrease glucose clearance. At the same time, insulin-sensitive tissues may also be responding less actively to insulin (partly as a result of glucose toxicity, but also partly through down-regulation of glucose transporters here too [5]), and hyperglycemia is exaggerated further.
One consequence of the need to maintain glucose disposal in such a situation is that glucose uptake will be increased secondary to the hyperglycemia in some tissues. However, few tissues can store glucose as glycogen, so in most cases, high concentrations of intracellular glucose derivatives simply drive glycolysis and other pathways of glucose metabolism. This may be of significance in driving intracellular abnormalities that lead to the acute and long term vascular abnormalities which characterize diabetes.

Thus, even in the absence of primary peripheral insulin insensitivity, excessive inadequate controlled hepatic glucose output may lead to a chain of escalating metabolic disturbances with serious adverse consequences. The current review espouses the essential role of the liver in maintaining glucose homeostasis, discusses its key involvement in the pathogenesis of Type 2 diabetes and considers the tools currently available to reduce hepatic insulin insensitivity as a principal component of Type 2 diabetes therapy.

Defining hepatic insulin insensitivity

The term ‘insulin insensitivity’ is usually conceived as impaired insulin-stimulated glucose disposal in the periphery. This error has a number of origins, but is most firmly embedded in the concept that the major action of insulin is to assist disposal of ingested carbohydrate through uptake into skeletal muscle. This conceptual error has been enhanced by characteristic measurement of ‘insulin sensitivity’ by the glucose clamp technique, where the insulin concentrations often used are such that, in non-diabetic people, hepatic glucose output is almost fully suppressed, and any difference measured will be secondary to differences in the sensitivity of peripheral tissues to insulin (abnormalities of glucose concentration-driven metabolism being neutralized by the unchanging glucose concentrations of the clamp) [6].

There are two major problems with this concept. The first is the definition of
‘sensitivity’ (or the more common, but less correct term ‘resistance’). In simple terms, a lower mass of insulin-sensitive tissue in the body should be associated with a decreased insulin response to a fixed dose of insulin. However, while it might be legitimate to say that the whole body response to insulin has decreased, it cannot be said that the responsiveness of skeletal muscle has changed. Although correcting insulin dose for body weight (as is usually done), might be thought to compensate for this, skeletal muscle mass (the major component of body weight in most people) does not vary directly in proportion to it. Even if the insulin dose is given per kilogram of skeletal muscle (or its surrogate fat free mass), problems of interpretation of the meaning of insulin sensitivity still arise.

Secondly, the concept fails to grasp the idea of insulin insensitivity in the context of the broader metabolic, tissue and organ dysfunction present in Type 2 diabetes — in particular, hepatic dysfunction. Insulin-stimulated glucose disposal in the periphery is just one component of insulin insensitivity, which also encompasses insulin-mediated processes in the liver, such as hepatic glucose output (HGO) and uptake (HGU), as well as clearance of insulin itself.

The failure of islet β-cells to compensate adequately for impaired insulin-stimulated glucose disposal is one of the principle mechanisms underlying the onset of hyperglycemia and overt Type 2 diabetes [7,8]. However, an accompanying rise in hepatic glucose output due to hepatic insulin insensitivity (at least in part) is a central component. In otherwise healthy individuals without diabetes, hyperinsulinemia would be expected to suppress HGO and lower blood glucose. In Type 2 diabetes, however, the onset of hyperglycemia (itself a potent inhibitor of HGO), together with hyperinsulinemia, indicates the presence of hepatic insulin insensitivity [9,10] (Figure 1). It has been postulated that hepatic insulin insensitivity (and the accompanying increase in HGO) is secondary to peripheral insulin insensitivity — i.e. a compensatory response to restore peripheral glucose uptake in the presence of peripheral
insulin insensitivity. However, recent evidence from studies in gene knockout mice supports the idea that the liver may also be a primary site of insulin insensitivity [11], suggesting the presence of intrinsic hepatic dysfunction in the pathogenesis of Type 2 diabetes. In either case, as increased HGO is central to the onset of hyperglycemia, it highlights the need to target hepatic insulin insensitivity as a central component in treating hyperglycemia.

**The liver and glucose homeostasis in the normal state**

In the healthy, non-diabetic individual, plasma glucose levels are a tightly controlled balance between glucose production and glucose utilization. The liver is responsible for providing 90% of the glucose to both insulin-insensitive and insulin-sensitive tissues in the fasting state [12], with over two-thirds of this being utilized by non-insulin-sensitive tissues (principally the central nervous system [CNS]), and the remainder by insulin-sensitive tissues (principally skeletal muscle) [13]. The liver is therefore the primary organ responsible for maintaining sufficient glucose levels and preventing hypoglycemia in the fasting state.

Glucose production is determined in approximately equal measure by the rates of gluconeogenesis and glycogenolysis in the immediate fasting state, although the role of hepatic glycogen becomes negligible with more prolonged fasting. Recycling of muscle glycogen via intermediary metabolism (the Cori cycle) serves to maintain the glucose levels necessary for the CNS [14]. Under fasting conditions where insulin levels are low, the principle hormonal mechanism maintaining glycemia involves stimulation of gluconeogenesis and glycogenolysis by basal levels of glucagon, although other hormonal and neural factors may also be involved. In the prandial state, on the other hand, the meal-related increase in insulin concentration (producing a high insulin/glucagon ratio) is the principle stimulus to suppress HGO by promoting glycogen synthesis and inhibiting glycogenolysis and
glnoneogenesis [15].

The dose–response curve relating plasma insulin to HGO reveals that the liver is sensitive to small increases in portal vein insulin concentrations [10] (Figure 1). The dose–response curve of insulin’s action on peripheral glucose uptake, however, shows it to be less effective in the periphery with EC$_{50}$ values double those for HGO [16]. Consequently, with low physiological increments in plasma insulin, the liver is the primary determinant of whole body glucose homeostasis. In both animal and human studies, low concentrations of insulin appear to inhibit HGO acutely through a rapid direct effect on glycogenolysis in the liver [17,18].

Again, it should be emphasized that non-hormonal mechanisms also play a key role in regulating physiological glucose levels in the prandial state. In response to physiological hyperglycemia, net HGO can be attenuated by 60–90% in the presence of basal insulin/glucagon concentrations [2]. Furthermore, non-esterified fatty acids (NEFA) can also inhibit insulin- and glucose-induced stimulation of muscle glucose uptake and suppression of HGO, as well as resetting hepatic autoregulation [19] and increasing the contribution of gluconeogenesis to HGO [20].

An indirect effect of insulin on HGO via inhibition of glycogenolysis/gluconeogenesis has been demonstrated in animals and humans — as expected this occurs more slowly and at higher insulin concentrations [17,18,21]. While it has been suggested that this indirect effect (which may occur via insulin-mediated inhibition of lipolysis in adipose tissue and reduction of the plasma NEFAs, or other adipose tissue, neural, pancreatic α-cell or muscle-derived effects) may be the major component of the suppressive effect of insulin on HGO in non-diabetic individuals, studies looking at the portal insulin signal in dogs suggest that direct effects are at least of equal significance and dominate in the basal state [22]. In fact, a recent study in dogs suggests that the direct effects are predominant [23]. Furthermore, in liver-
specific insulin receptor knockout mice, even high-dose insulin fails to suppress HGO. This indicates that both direct and indirect effects of insulin require an intact insulin-signalling pathway in the liver [24,25]. By contrast, muscle-specific insulin receptor knockout mice maintain normal fasting and post-challenge glucose homeostasis [25].

**Hepatic glucose uptake**

In healthy non-diabetic individuals, approximately one-third of an oral glucose load is taken up by muscle and fat, one-third by the liver (*via* insulin-dependent and independent mechanisms) and one-third by other non-insulin-dependent tissues [26]. This distribution, combined with the liver’s role in meal-related suppression of endogenous glucose production, emphasizes the central role that the liver plays in determining the extent of postprandial excursion of blood glucose concentrations, in addition to the regulation of fasting levels in the non-diabetic individual [26].

HGU (measured as splanchnic glucose uptake in humans) is less sensitive to insulin relative to its effects on HGO and less sensitive than peripheral glucose uptake. This suggests that different insulin signalling mechanisms exist within the liver [27]. However, as with the effects of insulin on HGO, approximately 50% of the effect of insulin on HGU appears to be a direct effect on the liver (associated with an increase in glycogen storage) and the remaining 50% an indirect effect (associated with increases in glycolysis and glucose oxidation) [28].

It should be mentioned that many other factors influence the effectiveness of insulin to control glucose uptake in the liver — in particular, hormone-independent autoregulation by glucose itself, which is synergistic with the effects of insulin, such that hyperinsulinemia by itself is relatively ineffective at promoting HGU and equally, the liver has a reduced ability to respond to hyperglycemia when insulin is deficient. However, unlike HGO, glucose uptake
generally only occurs in response to supraphysiological rather than physiological glucose levels. Whereas the glucose transporters (GLUT-1 and GLUT-2) in the liver do not depend on insulin for their translocation, insulin is probably involved in the autoregulatory response, through its ability to maintain glucokinase and glycogen synthase activity in the liver [2].

Fatty acids have also been shown to impair insulin-mediated HGU in healthy individuals [29]. In addition, studies in dogs suggest that high portal glucose levels relative to the periphery impart an inhibitory signal in non-hepatic tissues, particularly skeletal muscle. This reduces peripheral glucose disposal and thus directs glucose to the liver [30]; this effect appears to be neurally mediated. Furthermore, it has also been hypothesized that, in response to insulin, a factor is released from the liver that stimulates glucose uptake in skeletal muscle. In order for insulin to produce this effect, a parasympathetic permissive reflex that signals the presence of feeding must be present [31]. Mechanisms such as these may at least partially explain the differences in dose–response relationships between HGO in the liver and glucose disposal in the periphery. Finally, hypothalamic lipid-sensing via brain insulin receptors is proposed to regulate hepatic glucose metabolism via the activation of vagal efferent fibres that supply the liver [32].

**Key signaling pathways involved in glucose homeostasis in the liver**

Binding to the glucagon receptor on hepatocytes activates the serine/threonine kinase protein kinase A (PKA) causing phosphorylation and activation of glycogen phosphorylase kinase (GPK) and subsequently glycogen phosphorylase (GP), thus activating glycogenolysis. An increase in intracellular cyclic AMP also induces gluconeogenesis enzymes (phosphoenolpyruvate carboxykinase [PEPCK] and glucose-6-phosphatase [G6Pase]) via induction of peroxisome proliferator activated receptor-γ coactivator 1α (PGC-1α) [for
review see 33]. It should be emphasised, however, that under fasting conditions (potentially hypoglycemic conditions, in particular), non-hormonal mechanisms (principally hepatic autoregulation by glucose itself) are capable of supplying a significant proportion (up to 50%) of the body’s glucose requirements via enhancement of both glycogenolysis, glucose cycling and eventually gluconeogenesis) [2].

The pathways involved in insulin signalling in the liver are highly complex, involving hundreds of signaling molecules (reviewed in detail elsewhere [34,35], and thus a myriad of potential points for modulation and interaction with other pathways, such as those involved in glucose autoregulation. Insulin signalling processes also appear to differ in different tissues. The first key component in the signalling process is the insulin receptor itself and the associated intracellular insulin receptor substrate (IRS) proteins [35]. The IRS-2 subtype appears to play a more prominent role in the liver, whereas the IRS-1 subtype may be more important in skeletal muscle [36], and these two proteins have different capacities to interact with downstream signalling elements [37]. Within the liver, IRS-1 has been more closely linked with glucose homeostasis, whereas IRS-2 may be more closely liked with lipid metabolism [38], although surprisingly, liver-specific knockout of IRS-2 in mice does not appear to impair hepatic glucose and lipid metabolism [39]. The second key component involves the activation of the phosphatidylinositol 3-kinase (PI3K) pathway, which appears to be crucial for insulin’s metabolic actions in vivo in the liver [35,40] After PI3K activation, the specific regulation of glucose and lipid homeostasis by insulin in the liver diverges — PI3K-dependent activation of Akt (also known as protein kinase B [PKB]) appears to regulate factors involved in gluconeogenesis, whereas PI3K-dependent activation of atypical forms of protein kinase C appears to regulate factors involved in lipogenesis [40]. For instance, a pathway downstream of Akt leads to inactivation of phosphorylase, activation of glycogen synthase, and stimulation of glycogen synthesis, thus counteracting the effects of glucagon
In addition to acute effects on metabolic processes, insulin can also induce changes in gene transcription in the liver down-stream of the PI3K pathway [for reviews see 42, 43]. Insulin can influence the expression of over 150 genes — this occurs via key transcription factors, such as FOXO1 that inhibits expression of PEPCK and G6Pase and inhibits gluconeogenesis), sterol-response element binding proteins (SREBPs) that primarily regulate genes involved in lipid synthesis), and specificity protein 1 (Sp1) that regulates genes for insulin receptors and leptin).

**Insulin clearance in the liver**

The liver is also the primary site of insulin clearance, with approximately 50% of portal insulin being removed during first-pass transit, thus limiting hyperinsulinemia in the periphery [for review see 44]. As such, mean insulin concentrations in the portal vein are approximately twice as high as in the periphery and insulin pulse amplitude can be up to ten times higher [45]. Most uptake is a receptor-mediated process and prolonged increases in portal insulin levels result in reduced clearance due to receptor down-regulation [31]. Insulin sensitivity and clearance have been found to be directly and linearly correlated [46]. Uptake and degradation are also under the influence of mediators, such as NEFA (which has an inhibitory effect) [47].

**Insulin and hepatic fat metabolism**

A further direct action of insulin in the liver involves the metabolism of hepatic fat and production of triglyceride-rich very low-density lipoprotein (VLDL) [for review see 48]. Rates of hepatic VLDL secretion by the liver depend largely upon the partitioning of
preformed fatty acids between oxidation and esterification, and the retention or secretion by
the liver of synthesized triglycerides [48]. Insulin acutely inhibits VLDL production and this
effect may be modified by nutritional state — insulin secretion in a fed state may stimulate
hepatic VLDL-triglyceride secretion, whereas insulin secretion after a sufficiently long fast
may actually inhibit VLDL secretion [49]. This may play a role in regulating postprandial
lipemia, although as with glucose, this can only be fully understood in the context of the
peripheral tissues involved, principally adipose tissue and skeletal muscle. Disturbances in fat
metabolism in the liver (possibly due to oversupply of NEFA or reduced adiponectin levels),
leading to fatty infiltration (and thus fatty liver) may be an important factor in the
development of hepatic insulin insensitivity (see below) and diabetic dyslipidemia
(hypertriglyceridemia).

The liver as a central organ in the pathogenesis of diabetes

It is clear from the sections above that the liver and its response (either direct or indirect) to
insulin in particular, are critically involved in a complex set of processes that directly control
glucose levels also affected by glucose metabolism in the periphery (Table 1). In Type 2
diabetes, the excessive rate of HGO is generally considered to be the major abnormality
responsible for the elevated fasting plasma glucose (FPG) concentration and the defect in its
suppression a primary factor underlying postprandial hyperglycemia [50]. This may be
important to help to overcome decreased peripheral insulin sensitivity through the
compensatory mass action effect of hyperglycemia. However, reduced HGU may also
contribute to the fasting hyperglycemia of Type 2 diabetes by an insulin-dependent
mechanism and by altering glucose sensing within the hepatocyte (by disturbing
autoregulation), thereby disrupting the regulation of glucose release [4]. This attenuation of
glucose sensing in the liver only serves to put further burden on active hormone-dependent
processes in the struggle to restore adequate glucose homeostasis in Type 2 diabetes.

Hepatic insulin insensitivity in diabetes

In Type 2 diabetes, the onset of hyperglycemia (itself a potent inhibitor of HGO), alongside normo- or hyperinsulinemia, indicates the presence of hepatic insulin insensitivity. Severe hepatic insensitivity to insulin is observed at all plasma insulin concentrations throughout the physiological range [10]. The dose–response curves for both peripheral glucose uptake and HGO are shifted by an equivalent amount to the right in people with Type 2 diabetes, showing that both hepatic and peripheral insulin insensitivity are equally affected and that the higher relative sensitivity of the liver to insulin is maintained [16]. Nevertheless, recent studies in rodents suggest that insulin signalling alterations in insulin-resistant liver may be distinct from those reported for insulin-resistant skeletal muscle in animals and humans [51].

In addition to reduced suppression of HGO, hepatic insulin insensitivity also presents as a reduction in HGU. Due to the presence of marked insulin insensitivity in muscle, the relative contribution of HGU to overall glucose disposal is greater in people with diabetes, particularly while absolute insulin concentrations are raised. People with Type 2 diabetes are also insensitive to the acute inhibitory effect of insulin on VLDL production in the liver and insulin clearance rates are decreased [44].

The mechanisms underlying the development of hepatic insulin insensitivity are not well understood. It has been postulated that, due to the high sensitivity of the liver to insulin relative to peripheral tissues, small deficits in the β-cell response that occur early in the pathogenesis of diabetes could be responsible for increases in HGO [50]. This in turn could lead to glucose toxicity-induced peripheral insulin insensitivity [3] and compensatory hyperinsulinemia. Furthermore, it has been suggested that hepatic insulin insensitivity may be
the primary event in the development of whole-body insulin insensitivity associated with increased adiposity. Studies in dogs by Kim and colleagues [52] showed that increases in adiposity produce only a moderate defect in peripheral insulin sensitivity, but can produce a complete failure of insulin to suppress glucose production during a hyperinsulinemic-euglycemic clamp.

Whereas some authors suggest that people with Type 2 diabetes are primarily resistant to the direct hepatic suppressive effect of insulin (possibly mediated via glycogenolysis), with intact indirect peripherally mediated suppression of glucose production [53], others report that both indirect and direct effects are impaired with the greatest impairment seen in the indirect extrahepatic process, especially at high insulin levels [54]. In concert with these findings, there is evidence for both increased gluconeogenesis and accelerated glycogenolysis associated with increases in HGO [55].

The presence of excess liver fat is emerging as a key factor involved in the development of hepatic insulin insensitivity. Liver fat correlates with whole body and hepatic insulin resistance in people with and without diabetes [56] and also correlates with high insulin requirements [57]. Reducing hepatic fat content could therefore be a key target for therapies aimed at improving hepatic insulin sensitivity. Furthermore, the fatty liver is associated with overproduction of multiple cardiovascular risk factors (including PAI-1, C-reactive protein [CRP], fibrinogen, in addition to glucose and lipids) [58], and is therefore also a target for lowering cardiovascular risk. However, the causes of fat accumulation in the liver remain poorly understood. Changes in adipose tissue function resulting in NEFA oversupply and alterations in adipocytokine release (especially reduced adiponectin) are possible candidates [58]. For instance, adiponectin level is negatively associated with liver fat content and HGO in people with type 2 diabetes [59].

Certainly, several adipose tissue-associated factors appear to contribute to the complex
regulation of glucose homeostasis in the liver and abnormal circulating levels of NEFA, adiponectin and resistin (among others) are observed in people with diabetes. In particular, NEFAs are known to enhance HGO, impair insulin-mediated HGU and have been implicated in the development of both insulin insensitivity and Type 2 diabetes [29]. Elevated plasma NEFAs induce hepatic insulin insensitivity by inhibiting the insulin signal transduction system and abnormal insulin-mediated suppression of plasma NEFA appearance rate may be an early defect in those who develop Type 2 diabetes [60]. Furthermore, in the presence of hepatic insulin insensitivity, hepatic lipogenesis is increased. This raises VLDL production, which increases NEFA from adipose tissue leading to further escalation of VLDL production and an ensuing vicious circle.

In addition, people with Type 2 diabetes have characteristics of an inflammatory condition with increased levels of pro-inflammatory cytokines interleukin-6 (IL-6), interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α) and liver-derived acute-phase reactants, such as CRP and serum amyloid A (SAA) [for review see 15]. Subclinical chronic inflammation might be an important pathogenic factor in the development of insulin insensitivity and IL-6 can inhibit insulin receptor signal transduction in hepatocytes in culture and in livers of mice injected with IL-6, whereas TNF-α antagonizes insulin receptor signalling by promoting serine phosphorylation of IRS-1 and IRS-2.

**Hepatic dysfunction, insulin insensitivity and CVD**

Insulin insensitivity is now well established as a risk marker for cardiovascular disease (CVD). A number of cross-sectional studies have reported an association between insulin insensitivity and CVD risk in people with or without Type 2 diabetes and, more recently, longitudinal studies have added more weight to this association [61,62]. It is possible that
interventions that improve insulin sensitivity may improve CVD outcomes more than expected from glucose-lowering alone, as suggested with metformin in the UKPDS [63]. However, the recently reported results of the PROactive study have failed to confirm this expectation emphatically [64].

As part of the normal physiological maintenance of glucose homeostasis, compensatory fasting hyperinsulinemia is an inevitable consequence of underlying insulin insensitivity in muscle and adipose tissue, as long as sufficient residual islet β-cell function remains, especially in the earlier stages of Type 2 diabetes. However, not all tissues share the defect in insulin action, thus leading to the potential adverse impact of the compensatory hyperinsulinemia on tissues that remain normally insulin sensitive [65]. Many CVD risk factors, such as a dysregulated lipoprotein profile, endothelial dysfunction, procoagulant activity and vessel wall inflammation have been postulated as being secondary to this compensatory hyperinsulinemia [65]. Such a relationship may appear to be supported by a number of epidemiological and observational studies in which fasting hyperinsulinemia has been associated with increased CVD risk and mortality. However, the complexity of the relationship between hyperinsulinemia, insulin insensitivity and other CVD risk factors makes these factors hard to separate [for review see 65] and the magnitude of the relationships themselves is often too small to attribute causation with any confidence.

How much of this increased CVD risk is attributable specifically to hepatic insulin insensitivity remains undetermined. The relationship persists where measurements primarily assess hepatic insulin sensitivity (for example, using homeostasis model assessment [HOMA], see below), although this may mirror peripheral insulin sensitivity [62, 66]. Furthermore, CVD is associated with FPG level [67], which (as mentioned above) is determined primarily by glucose homeostasis in the liver. Certainly, components of diabetic dyslipidemia, which are themselves risk factors for CVD [68], can be attributed to hepatic insulin insensitivity. For
instance, insulin insensitivity in the liver will be a major determinant of both hepatic triglyceride accumulation and plasma triglyceride levels [69]. In addition, liver fat content is an independent marker of myocardial function and reduced coronary functional capacity [70].

Further support for the potential clinical impact of hepatic dysfunction and insulin insensitivity comes from measurements of CRP. This primarily liver-derived factor is a marker of subclinical inflammation that is independently related to insulin sensitivity [71], to increased risk of development of Type 2 diabetes [72] and to increased cardiovascular event risk, with an effect size exceeding that of LDL-cholesterol in the at-risk population [73].

**Assessing hepatic insulin resistance in clinical trials**

To evaluate the effects of insulin-sensitizing agents on insulin-mediated processes in the liver, it is necessary to measure hepatic insulin sensitivity reliably. This requires the quantification of parameters related to HGO and HGU occurring *in vivo* during fasting, during low-dose hyperinsulinemic clamps, or using other dynamic tests. The use of glucose tracers, sophisticated tissue-specific techniques (for example, positron emission tomography), proper (non-trivial) calculations and a significant experimental expertise are necessary [29,74,75]. In addition, other hormones such as glucagon, play a fundamental role in modulating HGO under some conditions. Accordingly, their effects need to be taken into account when interpreting study data or they may confound the calculation of a reliable index of hepatic insulin sensitivity [76].

In the absence of complex methodologies, hepatic insulin sensitivity can be extrapolated from the currently used methods to assess whole body insulin sensitivity, but this requires the assumption that the defect in insulin sensitivity in the liver and peripheral tissues is equivalent [77]. The glucose infusion rate during the steady-state phase of the glucose
clamp is usually achieved after 2–3 hours and assessed at sustained levels of marked hyperinsulinemia. Given that HGO is suppressed at these levels (even in insulin-insensitive individuals), differences in the glucose infusion rate largely reflect peripheral glucose uptake rather than hepatic balance. The other widely used test is the intravenous glucose tolerance test (IVGTT), but here too, the elevated blood glucose and insulin levels following the administration of the glucose bolus are likely to shut down HGO quickly [78]. Therefore differences in insulin sensitivity, measured over 3 hours again reflect mostly the peripheral processes.

Indeed, for calculations of HGO, tracers [79] and specific mathematical modelling [80] must be exploited. Problems of tracer methodology, the relative sensitivity of hepatic and peripheral insulin responsiveness and the narrow window between normal HGO and complete HGO suppression, make construction of reliable insulin dose–response curves for this parameter difficult.

The oral glucose tolerance test (OGTT) and recently the meal test have been widely used for their simplicity and because they mimic the every-day handling of nutrients. These tests appear to involve the liver in a more pronounced way, perhaps because of their slow dynamics. However, the liver is sensitive to the rate of glucose absorption and the lack of any method to quantify this source of glucose with sophisticated double-tracer techniques [81] means that changes found in an OGTT reflect peripheral rather than hepatic sensitivity, as well as β-cell dysfunction.

Finally, surrogate markers of insulin sensitivity can be calculated when just fasting glucose and insulin are available. HOMA appears to be a reasonable index for assessing insulin sensitivity within studies when a single insulin assay is used [82]. However, relationships of insulin sensitivity versus other variables are generally weak using this method [76]. The quick insulin sensitivity check index (QUICKI) is a log transformation of HOMA to
yield directly an insulin sensitivity index [83]. Since the liver is playing the fundamental role in glucose homeostasis in basal fasting conditions, these indices (HOMA, QUICKI) can be assumed with reasonable approximations to be markers of hepatic insulin sensitivity rather than peripheral insulin sensitivity. The accuracy of HOMA may be particularly limited in people with hyperglycemia [77]; nevertheless, it has become one of the standard tools used in large-scale trials, given the advantages of being simple and relatively inexpensive.

Recently, a study from the De Fronzo group [84] showed that, in subjects with impaired fasting glucose and/or impaired glucose tolerance, as well as in normo-tolerant individuals, the glucose clamp-derived total glucose disposal (peripheral insulin sensitivity) strongly correlated with OGTT-derived dynamic measurements of insulin sensitivity (Matsuda’s ISLcomp [85], Stumvoll’s MCRest [86], and Mari’s OGIS [87]), while HOMA correlated more strongly with the basal hepatic insulin resistance, assessed during the titrated glucose infusion. This study further confirms that surrogate fasting insulin resistance indices, such as HOMA or QUICKI, are indicative of hepatic insulin resistance.

The effect of oral glucose-lowering agents on hepatic function

Currently available glucose-lowering drugs with some effect on insulin sensitivity include the biguanides (principally metformin) and the thiazolidinediones (pioglitazone and rosiglitazone). In addition, some studies have used troglitazone, which is no longer clinically available. Thiazolidinediones are agonists for the peroxisome proliferator-activated receptor gamma (PPARγ), which regulates multiple genes controlling carbohydrate and lipid metabolism [88].

Metformin
The molecular mechanisms that explain the clinical effects of metformin remain poorly understood, although it seems clear that biguanides can inhibit the early steps of gluconeogenesis and, in higher concentrations, this explains metformin’s propensity to cause lactic acidosis. In the basal, post-absorptive state, the improvement of fasting hyperglycemia with metformin is mostly due to a decrease of the elevated HGO [for review see 89], resulting from direct inhibition of gluconeogenesis and possibly glycogenolysis in the liver. A recent systematic review of clinical studies by Natali and Ferrannini suggests that, whereas metformin can enhance insulin suppression of HGO and FPG clearance (assessed using tracer glucose techniques), it does not appear to improve peripheral glucose disposal (assessed using the euglycaemic–hyperinsulinaemic clamp) [90].

Although its cellular mechanism of action in the liver remains poorly defined, a recent study demonstrates that metformin’s effects in the liver include insulin receptor activation, followed by selective IRS-2 activation and increased glucose uptake via increased GLUT-1 translocation [91]. Another key component may be stimulation of AMP-activated protein kinase (AMPK), which plays a critical role in systemic energy balance and may mediate the activity of adipokines in regulating glucose and lipid homeostasis [92]. Activation of AMPK appears to be necessary for metformin’s inhibitory effect on glucose production by hepatocytes [93], and metformin cannot lower blood glucose levels in mice that lack hepatic LKB1, which is an upstream kinase in the AMPK cascade [94, 95].

Some reported effects on peripheral glucose disposal may reflect overall improvements in glycemia (decrease in glucose toxicity) and metformin has been shown to facilitate glucose transporter trafficking in peripheral tissues. In the fed condition, metformin may also be affecting gut uptake of nutrients. However, an effect on gluconeogenesis in the fasting state would be expected to restore towards normal hepatic autoregulation of glucose handling. This effect might be interpreted as improved insulin responsiveness in a low-dose
insulin clamp.

**Thiazolidinediones**

Evidence from animal studies shows that the thiazolidinediones improve hepatic insulin sensitivity, as well as peripheral insulin sensitivity. Thus, administration of thiazolidinediones with a low dose of insulin restores HGO towards normal levels in streptozotocin-induced diabetic rats [96]. Similarly, whereas recombinant human growth hormone (rhGH) inhibits suppression of HGO in rats, this is restored when troglitazone is co-administered with rhGH [97]. Furthermore, troglitazone selectively decreased HGO in a spontaneous, non-obese, normolipemic rat model of Type 2 diabetes independently of its action on peripheral insulin sensitivity [98]. In addition, studies using isolated perfused liver from a rat model of Type 2 diabetes suggest that pioglitazone can directly increase hepatic insulin sensitivity *in situ* in the liver [99]. At the hepatic cellular level, PPARγ activation decreases the expression of several genes involved in gluconeogenesis (PEPCK, pyruvate carboxylase, and glucose-6-phosphatase) [100], and also upregulates other genes such as hormone sensitive lipase (*via* Sp1), which plays an important role in lipid mobilisation and may be involved in the development of insulin insensitivity when deficient [101]. Recent studies also suggests that thiazolidinediones may activate AMPK directly in the liver and also have direct anti-inflammatory effects in hepatocytes [102,103].

The primary site of thiazolidinedione action, however, remains controversial. PPARγ is expressed abundantly in adipose tissue, whereas expression is low in liver and muscle. This in itself might suggest that the hepatic effects are secondary to changes in NEFA or triglyceride metabolism. Data from knockout mouse models shed some light on this. Selective knockout of PPARγ in adipose tissue causes fatty liver, increased liver gluconeogenesis and a
decreased response to insulin action on HGO, but does not induce insulin insensitivity in muscle [104]. This could either indicate an indirect adipose tissue-related influence of PPARγ activation on the liver, or a direct effect on liver, which might seem less likely given the low level of PPARγ expression in the liver (Figure 2). However, treatment with a thiazolidinedione in these animals (with preserved liver PPARγ) improves insulin suppression of HGO, supporting the presence of a direct activation component in the liver itself. Similarly, muscle PPARγ-deficient mice also develop hepatic insulin insensitivity, but not muscle insensitivity, and this is accompanied by increased adiposity — these mice also respond to thiazolidinediones [105]. These studies suggest that thiazolidinediones improve insulin sensitivity by direct actions on tissues other than skeletal muscle (i.e. adipose tissue and possibly liver) and that, in the absence of adipose tissue, the liver becomes the primary site of thiazolidinedione action [88]. This is supported by studies in lipoatrophic mice, where inactivation of liver PPARγ reduces hepatic steatosis, but worsens the hyperlipidemia, triglyceride clearance and interestingly muscle insulin sensitivity, in addition to abolishing the hypoglycemic and hypolipidemic effects of rosiglitazone [106]. Furthermore, a recent study in liver-specific insulin receptor knockout mice suggests that, whereas thiazolidinediones probably improve some lipid parameters even in the presence of absolute hepatic insulin insensitivity, both metformin and thiazolidinediones require an operating insulin-signalling system in the liver for their effects in glucose homeostasis [107].

Studies using the euglycemic insulin clamp and frequently sampled IVGTT in people with Type 2 diabetes have extended insights on the mechanism of action of thiazolidinediones to a more clinically relevant level. The systematic review by Natali and Ferrannini suggests that, unlike metformin, thiazolidinediones improve peripheral glucose disposal in addition to enhancing insulin suppression of HGO and FPG clearance [90]. Pioglitazone therapy in people with Type 2 diabetes decreases both fasting and postprandial plasma glucose levels by
improving whole-body insulin sensitivity and, more specifically, both insulin-mediated suppression of HGO and peripheral glucose uptake in a dose-dependent manner [6,108,109]. Recent studies suggest that both pioglitazone and rosiglitazone decrease FPG via an inhibition of gluconeogenesis in the liver [110, 111]. Furthermore, pioglitazone also augments splanchnic (i.e. hepatic) glucose uptake [109] and dose-dependently enhances islet β-cell function [108]. Recent studies also show that rosiglitazone can increase hepatic insulin clearance in people with type 2 diabetes [112, 113].

A shift of fat distribution from visceral to subcutaneous adipose depots after pioglitazone treatment is associated with improvements in hepatic and peripheral tissue sensitivity to insulin [114]. Indeed, pioglitazone treatment in Type 2 diabetes decreases hepatic fat content [109]. This could be secondary to decreased NEFA supply and, as noted above, might itself reverse improved hepatic glucose metabolism and thus appear to reverse hepatic insulin insensitivity. These studies also suggest a role for adipokines in the mechanism of action of thiazolidinediones. Thus, the increase in plasma adiponectin concentration seen after thiazolidinedione therapy may play an important role in reversing the abnormality in hepatic fat mobilization and the hepatic/muscle insulin insensitivity in people with Type 2 diabetes [59]. Recent studies in adiponectin-deficient knockout mice suggest that activation of AMPK may be involved in the adiponectin-dependent effects of thiazolidinediones in the liver [115, 116]. Rosiglitazone has also been shown to increase the expression of the adiponectin ADIPOR2 receptor subtype in mouse hepatocytes, which may increase liver sensitivity to adiponectin and synergize with the adiponectin-raising effects [117]. On the other hand, a decrease in plasma resistin is positively correlated with the decrease in hepatic fat content and improvement in hepatic insulin sensitivity seen with pioglitazone [118].

These studies also provide head-to-head comparisons of thiazolidinediones with
metformin, revealing differences in pattern of action. Recently, Tiikkainen and colleagues [112] found that metformin and rosiglitazone both improved hepatic insulin sensitivity in people with Type 2 diabetes, though to a different extent. However, only rosiglitazone treatment produced a reduction in liver fat content. Furthermore, only rosiglitazone increased peripheral glucose uptake and PPARγ, lipoprotein lipase and adiponectin expression in adipose tissue.

Further support for the hepatic action of thiazolidinediones comes from their effects on levels of CRP. Thiazolidinediones significantly reduce CRP levels in people with the metabolic syndrome [119] and in those with Type 2 diabetes [120] and rapidly improves both CRP and serum amyloid A (SAA) levels in healthy individuals [121]. Improving glycemic control with sulfonylureas, however, does not influence CRP levels [122]. While metformin can also reduce CRP levels by 30% in diabetes, it is only half as effective as troglitazone over 4 months of treatment [120] and not all studies have been able to demonstrate an effect of metformin on CRP [123]. Furthermore, a recent meta-analysis of four 1-year studies with pioglitazone in people with Type 2 diabetes shows a consistent reduction in alanine aminotransferase (ALT) levels (a marker of fatty liver disease [124]), suggesting potential beneficial effects on liver function, whereas metformin showed small increases or decreases and gliclazide showed consistent increases [125].

**Effects on insulin sensitivity in clinical trials**

Several short-term studies have confirmed the beneficial effects of the thiazolidinediones in improving insulin sensitivity as measured using the HOMA, a test which, as described above, primarily assesses hepatic insulin sensitivity. In a 12-week study in 330 people with Type 2 diabetes, troglitazone significantly improved insulin sensitivity and lowered fasting plasma insulin levels compared with placebo [126]. Similarly, rosiglitazone significantly improved
insulin sensitivity among people with Type 2 diabetes treated for 12 weeks [127] and 26 weeks [128]. Several studies have also demonstrated an improvement with pioglitazone either as monotherapy or in combination with a sulfonylurea or metformin. In a 16-week study in people with Type 2 diabetes, pioglitazone therapy (30 or 45 mg/day) resulted in significant reductions in fasting serum insulin levels and increased insulin sensitivity versus placebo [129]. Pioglitazone monotherapy significantly improved insulin sensitivity and improved islet β-cell function among people with Type 2 diabetes treated for 23 weeks in a study that also demonstrated a reduction in several risk markers for CVD [130]. A further 16-week study in people with Type 2 diabetes found that those with poorer insulin sensitivity or preserved islet β-cell function at baseline experienced greater improvements in glycemic control with pioglitazone than with metformin [131]. Significant improvements versus placebo in insulin sensitivity, as measured using either the HOMA or the QUICKI, were also seen in a meta-analysis of data from three placebo-controlled registration studies that included approximately 1000 people with Type 2 diabetes [132]. Improvements versus placebo were seen for those treated with pioglitazone as monotherapy as well as among those who received pioglitazone in combination with a sulfonylurea or metformin [132]. A 32-week study in people with Type 2 diabetes revealed potential differences between pioglitazone and metformin in terms of their ability to improve insulin sensitivity [133]. While both agents improved glycemic control, people treated with pioglitazone experienced more pronounced improvements in insulin sensitivity compared with those who received metformin monotherapy [133]. At study endpoint, HOMA insulin sensitivity was increased from baseline by 15% with pioglitazone (p<0.005), whereas there was no difference from baseline with metformin (−1%), with a significant between-group difference (p<0.05).

Studies comparing addition of rosiglitazone to existing metformin therapy versus uptitration of metformin show significantly greater improvement in HOMA insulin sensitivity
Two 2-year studies have compared the effects on HOMA-%S, fasting serum insulin, C-peptide and insulin precursors of: 1) pioglitazone versus metformin when added to existing sulfonylurea therapy; and 2) pioglitazone versus gliclazide when added to existing metformin therapy [138]. Sustained improvements in glycemic control (HbA$_1c$ and FPG) with pioglitazone or metformin were accompanied by sustained improvements in fasting insulin and C-peptide levels, which translated to an improvement of HOMA-%S (7.1–11.8% with pioglitazone; 5% with metformin). Conversely, gliclazide was associated with increased fasting insulin and improvements in FPG that were not sustained and no change in HOMA-%S. These data show that pioglitazone or metformin treatment produces long-term improvements in FPG and insulin sensitivity, most likely reflecting improved hepatic insulin sensitivity.

As the mode of effect of metformin is generally considered to be a direct effect on HGO, at least in the fasting state, it is not surprising that metformin has consistently been demonstrated to cause a reduction in FPG [89]. If the action of thiazolidinediones is primarily to affect liver insulin sensitivity (either directly or indirectly), then they might also be expected to have a greater effect on FPG relative to postprandial plasma glucose, due to the liver’s predominant role in controlling FPG, compared with its shared role in controlling glucose disposal. At least some impact on postprandial glucose is still likely as, in Type 2 diabetes, the absolute postprandial levels of glycemia are mainly dependent upon HGO and absolute glucose disposal is generally unchanged compared with non-diabetics — rather it is just inappropriate for the overall levels of glycemia due to insulin insensitivity [139]. On the other hand, as the
greater proportion of glucose uptake in the fasting state in Type 2 diabetes is not insulin sensitive [13], an effect primarily on peripheral insulin sensitivity to increase peripheral glucose disposal should, for the most part, affect postprandial glucose. A review of recent clinical trials clearly demonstrates a consistent reduction in FPG with thiazolidinediones (Table 1), supporting a hepatic site of action [129,132,134,136,137,140–152].

Studies in people with other medical conditions

Further support for a hepatic site of action for metformin and the thiazolidinediones is provided from studies in people conditions other than diabetes, including non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH), and polycystic ovary syndrome (PCOS), both of which are generally characterized by the presence of insulin insensitivity (a significant component of which has been shown specifically to be hepatic insulin insensitivity [153]), and lipodystrophy syndromes.

Non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH)

Insulin insensitivity appears to be the most reproducible predisposing factor for NAFLD, prompting trials of insulin-sensitizing drugs in this patient group [154]. Small trials with metformin or thiazolidinediones reveal improvements in measures of hepatic function in people with NAFLD or NASH [for review see 155]. Bugianesi and colleagues showed that 12 months’ treatment with metformin in patients with NAFLD (n=110) significantly improved the chances of having a normal ALT compared with a prescriptive diet or vitamin E treatment [156]. Metformin also significantly improved HOMA insulin sensitivity compared with diet. A control biopsy of 17 metformin-treated patients also showed significant reductions in liver fat, necroinflammation, and fibrosis. In a study in 36 patients with NASH, metformin
significantly improved ALT, aspartate aminotransferase (AST), and HOMA compared with diet alone [157]. The first randomized, double-blind, placebo-controlled trial to examine the role of a thiazolidinedione (pioglitazone) in NASH (n=55) showed that pioglitazone treatment for 6 months significantly improved multiple metabolic and histological abnormalities compared with diet alone [158]. Hepatic insulin sensitivity was improved, ALT and AST levels were decreased, liver fat content reduced by 50%, hepatic inflammation reduced, and combined pathological score improved. Adiponectin levels significantly increased and were inversely correlated with the reduction in hepatic fat. The results of several small studies support these observations. In one study, troglitazone treatment over 3–6 months produced normalization of ALT in 7 of 10 participants and improved inflammation in 4 participants at follow-up [159]. In another study over 48 weeks, rosiglitazone treatment in 30 people improved insulin sensitivity and histological markers of NASH [160]. Finally, a 1-year study with pioglitazone in 18 NASH patients without diabetes also resulted in significant improvements in insulin sensitivity, serum ALT and histological features [161]. In addition, a small pilot study has shown that a combination of vitamin E and pioglitazone produces a greater improvement in NASH histology compared with vitamin E alone [162].

**Polycystic ovary syndrome [PCOS]**

Metformin is widely used off-label for the treatment of anovulation in women with PCOS and has been shown to improve insulin sensitivity and hormone patterns, as well as ovulation and pregnancy rates in numerous small trials [163]. In a recent large scale study, extended release metformin significantly improved HOMA insulin sensitivity, but did not appear to have any additional impact on fertility outcomes when added to the estrogen antagonist clomiphene [164]. The impact of metformin on HOMA in PCOS patients has been shown to persist over 4 years of therapy [165]. Thiazolidinediones appear to have similar benefits to metformin in this
patient group, although experience is much more limited [166], Rosiglitazone treatment for 3 months significantly improved HOMA insulin sensitivity in women with PCOS [167]. Treatment with pioglitazone (median 10 months) also significantly improved HOMA insulin sensitivity in women with PCOS not responding to metformin [168]. Tarkun and colleagues [169] showed significant decreases in CRP levels and improvements in HOMA insulin sensitivity with 12 months of rosiglitazone therapy in non-obese young women with PCOS. In a more recent placebo-controlled study, rosiglitazone significantly reduced CRP levels and ALT activity, and had beneficial effects on adiponectin and resistin levels in overweight women with PCOS [170, 171].

Lipoatrophy/lipodystrophy syndromes

The use of antiviral therapy containing protease inhibitors in people with HIV is also associated with lipodystrophy, insulin resistance, and glucose intolerance [for review see 172. Although these patients have decreased subcutaneous fat, they have more intra-abdominal and liver fat compared with non-HIV controls and have elevated ALT [173]. In a small placebo-controlled study in this patient group, rosiglitazone treatment for 24 weeks significantly decreased percent liver fat and normalized ALT [173]. Furthermore, in antiviral therapy lipodystrophy patients, PAI-1 concentrations, which correlate closely with increased liver fat (but not the size of other fat deposits) are decreased, together with a reduction in liver fat after 24 weeks of rosiglitazone treatment [174]. In addition, rosiglitazone has been shown to increase adiponectin and decrease resistin levels in these patients [175]. An earlier study in patients with a range of non-antiviral-induced lipoatrophy and lipodystrophy syndromes showed that after 6 months of troglitazone therapy, there was a selective increase in subcutaneous adipose tissue and a significant reduction in the size of the liver, suggesting a shift in fat storage from the liver to the periphery [176]. A recent study suggests that both
rosiglitazone and metformin improve HOMA insulin sensitivity to a similar extent in this patient group [177].

**Summary and Conclusions**

The processes governing glucose homeostasis in the liver, particularly those involved in insulin signalling, are complex and highly coordinated. It is clear that hepatic dysfunction (and HGO) is central to the pathogenesis of hyperglycemia in Type 2 diabetes, although the pathophysiological mechanisms underlying the dysfunction remain uncertain. It is most easily assessed as hepatic insulin insensitivity, and this remains a key target of glucose-lowering therapy. It is now clearly established that thiazolidinediones and metformin both improve hepatic insulin action and reduce HGO. Whereas metformin’s main mechanism of action in the liver appears to be a direct effect on HGO that may involve AMPK, multiple hepatic and extrahepatic mechanisms may be present for thiazolidinediones, including effects on adipokines (especially adiponectin), NEFA levels, and altered gene expression in hepatocytes (affecting gluconeogenesis and fat mobilization). Evidence from several sources, including knockout mice and clinical studies now supports a primary effect of thiazolidinediones in the liver. Whether this is mainly direct or indirect (*via* effects in adipose tissue and muscle) and the extent of the contribution from the hepatic component to overall glucose homeostasis remains to be clarified definitively.
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**Table 1 Components of glucose metabolism contributing to hyperglycemia**

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<tr>
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<th>Manifestation</th>
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<td>Liver</td>
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<td>non-suppressed glucose output</td>
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<tr>
<td></td>
<td>insulin insensitivity</td>
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<td>lost sensitivity to hyperglycemia</td>
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<td>lost hepatic autoregulation</td>
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<td>glucose insensitivity</td>
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<tr>
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<td>unchanged glucose uptake</td>
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<tr>
<td>Non-insulin sensitive</td>
<td>decreased glucose clearance</td>
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<tr>
<td>[brain and others]</td>
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Table 2 Change in FPG with thiazolidinediones in large-scale (n≥200), double-blind, randomised, controlled, ≥16 weeks’ duration studies

<table>
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<tr>
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<th>ΔFPG (% change)</th>
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<td>-29.1 vs Glic</td>
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<td></td>
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<td>Treatment</td>
<td>Change vs Control</td>
<td>Change vs Placebo</td>
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Glic=gliclazide; Glib=glibenclamide; Glim=glimepiride; Met=metformin; Nat=nateglinide;
Pbo=placebo; Pio=pioglitazone; Rosi=rosiglitazone; SU=sulfonylurea; Trog=troglitazone
Fig. 1 Hepatic insulin insensitivity in Type 2 diabetes. Hepatic glucose output is increased, despite hyperglycemia [panel A; Jeng et al, 1994; open circles = control subjects; closed circles = people with Type 2 diabetes] and hyperinsulinemia [panel B; Groop et al, 1989; broken line = non-obese Type 2 diabetes; solid line = matched control subjects mean ± SEM *p<0.05, **p<0.01 versus control subjects].

Fig. 2 Thiazolidinediones may improve many aspects of hepatic dysfunction through multiple mechanisms.