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For debate

Pathogenesis of Type 2 (non-insulin dependent) diabetes mellitus: a balanced overview*

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Following an overnight fast the majority of glucose disposal occurs in insulin-independent tissues, the brain (~50%) and splanchnic organs (~25%), while only 25% occurs in insulin-dependent tissues, primarily muscle [1–4]. Basal glucose utilization (~2 $mg \cdot kg^{-1} \cdot min^{-1}$) is precisely matched by glucose production by the liver [1–4]. Following glucose ingestion, the balance between uptake and output is disrupted and maintenance of glucose homeostasis depends upon three processes that must occur in a co-ordinated fashion: (1) *insulin secretion;* (2) stimulation of *glucose uptake* by splanchnic (liver and gut) and peripheral (primarily muscle) tissues in response to hyperinsulinaemia plus hyperglycaemia; (3) *suppression of hepatic glucose production.* It logically follows that abnormalities at the level of the Beta cell, muscle, and/or liver can lead to the development of glucose intolerance. The full blown syndrome of Type 2 (non-insulin-dependent) diabetes mellitus requires the simultaneous presence of two defects, *insulin resistance* and *impaired Beta-cell function.* In Type 2 diabetes the primary or inherited defect most likely represents impaired tissue (muscle and/or liver) sensitivity to insulin. Eventually, however, the Beta cell fails to maintain a sufficiently high rate of insulin secretion to compensate for the insulin resistance, and overt diabetes mellitus ensues.

Insulin secretion in Type 2 (non-insulin-dependent) diabetes

Study of Beta-cell function in Type 2 diabetes has demonstrated a consistent pattern which reveals a complex interplay between insulin secretion and insulin sensitivity. In individuals with impaired glucose tolerance (IGT) and mild diabetes, the fasting plasma insulin concentration is invariably increased and basal insulin secretion is enhanced [5–7] (Fig. 1). As the fasting glucose increases from 4.5 to 7.8 mmol/l (80 to 140 mg/dl) fasting plasma insulin progressively rises. When the fasting glucose exceeds 7.8 mmol/l (140 mg/dl), insulin secretion drops off precipitously (Fig. 1). The inability of the pancreas to maintain its high rate of insulin secretion has important pathophysiologic implications, since it is at this point (fasting glucose = 7.8 mmol/l = 140 mg/dl) that hepatic glucose production increases in absolute terms and begins to contribute to the elevation in fasting plasma glucose [7]. In Type 2 diabetic subjects, when glucose-stimulated insulin secretion is plotted against the fasting glucose, the same inverted "U" shaped curve is observed [1] (Fig. 2).

The pancreatic function curves displayed in Figures 1 and 2 are consistent with the natural history of IGT and Type 2 diabetes in man [1, 8–13] and in the rhesus monkey [14, 15] (Fig. 2). Even before the development of IGT, insulin resistance is well-established (Fig. 2). Progression from normal to IGT to Type 2 diabetes with mild fasting hyperglycaemia (6.7 to 7.8 mmol/l = 120 to 140 mg/dl) is associated with a marked increase in both fasting and glucose-stimulated plasma insulin levels [1, 8, 9, 13] (Fig. 2). Overt fasting hyperglycaemia (> 7.8 mmol/l = 140 mg/dl) results from an inability of the Beta cell to maintain its high rate of insulin secretion (Fig. 2). A similar pattern of insulin secretion occurs during the development of diabetes in the Rhesus monkey [14, 15]. These studies [1, 9, 10, 12, 13–16] conclusively document that hyperinsulinaemia precedes Type 2 diabetes and exclude the possibility that insulinopoenia initiates the process of diabetes. Studies in ethnic groups at high risk of developing Type 2 diabetes [8, 9, 16–20] and in first-degree relatives of Type 2 diabetic individuals [18, 21, 22] also document that hyperinsulinaemia predicts the development of Type 2 diabetes.

In summary, the earliest stages of Type 2 diabetes are characterized by augmented insulin secretion, which represents a compensatory response to insulin resistance.

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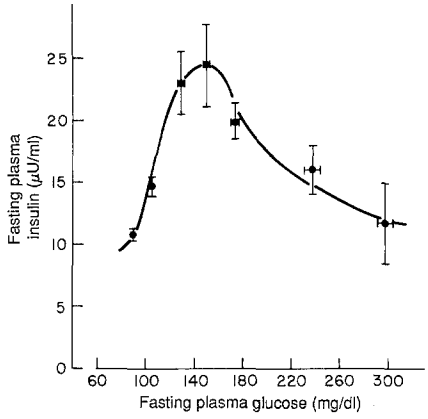

Fig. 1. Relationship between fasting plasma glucose concentration and fasting plasma insulin concentration in normal weight control subjects, in individuals with impaired glucose tolerance, and in Type 2 (non-insulin-dependent) diabetic subjects with varying degrees of fasting hyperglycaemia. As fasting plasma glucose concentration rises from baseline to 7.8 mmol/l (140 mg/dl) there is a progressive increase in the fasting insulin concentration. Thereafter, further rises in the fasting glucose are associated with a progressive decline in fasting insulin. In diabetic subjects with fasting glucose concentrations in excess of 11.1–12.2 mmol/l (200–220 mg/dl), fasting insulin declines to values observed in control subjects. Reproduced from reference 7 with permission

The cause of late-onset Beta-cell failure remains unknown. Beta-cell mass is only modestly reduced (by 20–40%) [23, 24] and genetic mutations of the insulin gene are uncommon [25]. A likely explanation for the acquired defect in insulin secretion relates to the concept of "glucose toxicity", in which chronic sustained hyperglycaemia in a (genetically) predisposed Beta cell leads to impaired insulin secretion [1, 26, 27].

We now shall shift from the pancreas to the insulin sensitive tissues, muscle and liver. However, we shall return to the Beta cell to examine the dynamic interaction between insulin action and insulin secretion [1, 7–9, 12, 15, 21, 28–30], since it is the disruption of this finely regulated balance which leads to the development of overt diabetes mellitus.

Insulin resistance in Type 2 diabetes

Longitudinal and cross-sectional studies have conclusively documented that hyperinsulinaemia antedates the development of Type 2 diabetes [1, 8–21, 31, 32], and studies employing the euglycaemic insulin clamp have demonstrated that progression from normal to IGT is associated with the development of severe insulin resistance [1, 8, 9, 13–15, 21]. The defect in insulin action is seen at all plasma insulin concentrations spanning the physiologic and pharmacologic range [33–35]. These observations provide convincing evidence that insulin resistance, not impaired insulin secretion, initiates the process of Type 2 diabetes in man.

Site of insulin resistance

Following the stimulation of insulin secretion, whole body glucose homeostasis is dependent upon three tightly coupled mechanisms: (1) suppression of *hepatic glucose production;* (2) augmentation of *splanchnic* (hepatic plus gastrointestinal) glucose uptake; (3) stimulation of glucose disposal by *peripheral tissues,* primarily muscle. The contribution of each of these processes to the insulin resistance in Type 2 diabetes will be reviewed.

Hepatic glucose production (HGP)

De Fronzo et al. have shown that the liver of healthy subjects produces glucose at ~1.8–2.2 $mg \cdot kg^{-1} \cdot min^{-1}$ in the postabsorptive state [1, 2, 4, 33, 36–41]. Type 2 diabetic subjects with *moderate fasting hyperglycaemia* demonstrate a consistent increase (~0.5 $mg \cdot kg^{-1} \cdot min^{-1}$) in basal HGP (Fig. 3), which is closely correlated ($r = 0.847$, $p < 0.001$) with the degree of fasting hyperglycaemia [1, 2, 4, 33, 36–41]. When extrapolated over 24 h the liver of a 70 kg patient with mild diabetes produces an additional 50 g of glucose each day. These results indicate that in Type 2 diabetic individuals with *overt fasting hyperglycaemia* (> 7.8 mmol/l = 140 mg/dl) excessive HGP is an important determinant of fasting hyperglycaemia. Similar results have been published by others [15, 30, 34, 35, 42–45]. In the postabsorptive state, plasma insulin concentration is increased 2–3 fold in diabetic individuals [1, 2, 4, 7, 33, 36–41] (Fig. 1). Since hyperinsulinaemia is a powerful inhibitor of HGP [1, 2, 33, 46], it is clear that *hepatic resistance* to insulin is present and contributes to the excessive basal output of glucose by the liver. In response to insulin, suppression of HGP is impaired in Type 2 diabetic patients with moderate to severe fasting hyperglycaemia [33–35] but this defect is less evident in diabetic

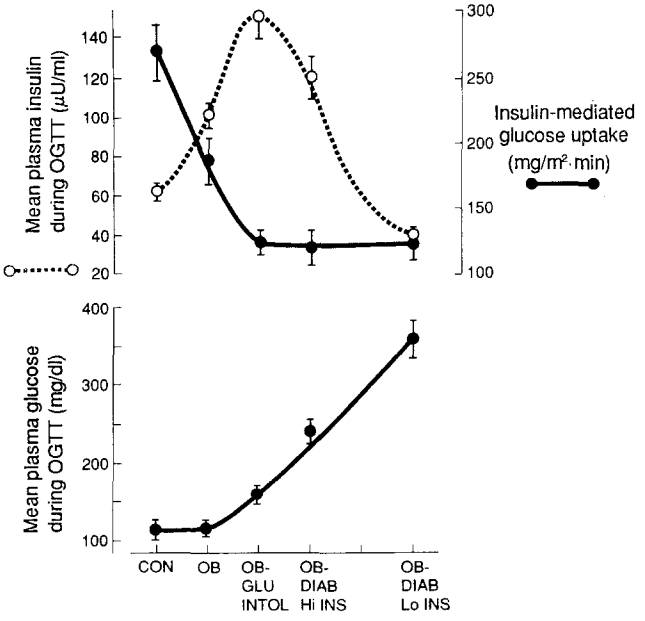

Fig. 2. Summary of the plasma glucose (bottom panel) and plasma insulin (top panel, open circles) responses during 100 g OGTT and tissue sensitivity to insulin (top panel, closed circles) in control, obese non-diabetic, obese glucose intolerant, obese hyperinsulinaemic diabetic, and obese hypoinsulinaemic diabetic subjects. See text for a detailed discussion. Reproduced from reference 1 with permission

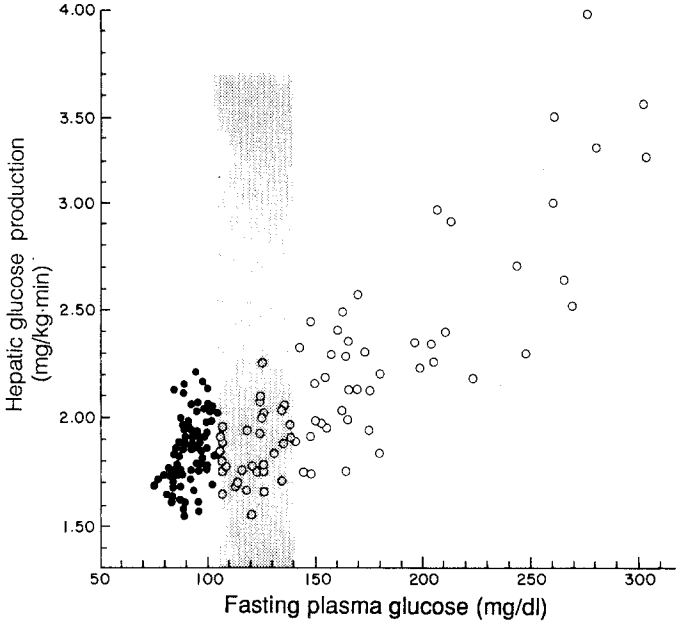

Fig. 3. Summary of hepatic glucose production in 77 normal weight Type 2 (non-insulin-dependent) diabetic subjects (open circles) with fasting plasma glucose concentration ranging from 5.8 to 16.7 mmol/l (105 to 300 mg/dl). Seventy-two age- and weight-matched control subjects are indicated by the closed circles. In the 33 diabetic subjects with fasting plasma glucose levels below 7.8 mmol/l (140 mg/dl) (shaded area), the mean rate of hepatic glucose production was identical to control subjects. In diabetic subjects with fasting plasma glucose concentration above 7.8 mmol/l (140 mg/dl), there was a progressive rise in hepatic glucose production that correlated closely ($r = 0.847, p < 0.001$) with the fasting plasma glucose concentration. Reproduced from reference 1 with permission

patients with mild fasting hyperglycaemia [1, 2, 4, 36–41]. From the quantitative standpoint, however, impaired suppression of HGP can account for only a small percentage (5–10%) of the defect in whole body glucose metabolism during an englycaemic insulin clamp study [1, 2, 4, 33–41].

Splanchnic (hepatic) glucose uptake

Employing hepatic vein catheterization, DeFronzo et al. [4] have documented net glucose release from the splanchnic area in the postabsorptive state in both control and Type 2 diabetic subjects, reflecting glucose production by liver. In response to insulin there was a prompt suppression of splanchnic glucose output (reflecting the inhibition of HGP) and after 2 h there was a small net splanchnic uptake of glucose, which averaged ~0.5 $mg \cdot kg^{-1} \cdot min^{-1}$ in both control and diabetic subjects. These results demonstrate that impaired splanchnic (liver plus gut) glucose uptake cannot explain the insulin resistance observed in Type 2 diabetic subjects under *euglycaemic hyperinsulinaemic* conditions.

Peripheral (muscle) glucose uptake

Using the insulin clamp technique with femoral vein/artery catheterization to quantitate leg glucose exchange, muscle tissue has been shown to be the primary site of insulin resistance under euglycaemic conditions. In response to insulin leg glucose uptake promptly increased ~10-fold in control subjects [4]. In contrast, in Type 2 diabetic subjects the onset of insulin action was markedly delayed and leg glucose uptake was decreased by 40–50% [4]. Similar results have been reported using the forearm catheterization technique [47–55]. Since in man adipocytes are quite inert [56], the primary leg and forearm tissue responsible for glucose removal must be muscle and it can be calculated that impaired muscle glucose uptake accounts for the great majority (~90%) of the decrease in total body glucose disposal during an insulin clamp study in Type 2 diabetic subjects [1, 4].

Glucose disposal during oral glucose tolerance test (OGTT)

The normal route of glucose entry is via the gastrointestinal tract. Employing hepatic vein catheterization with a dual isotope technique, Ferrannini et al. [57] have examined the contribution of splanchnic and peripheral tissues to glucose disposal in healthy subjects (Table 1). During 3.5 h following glucose (68 g) ingestion: (1) 19 g or 28% of the oral load was taken up by splanchnic tissues, (2) 48 g or 71% was disposed of by peripheral tissues; (3) of the 48 g taken up by peripheral tissues, the brain (an insulin-independent tissue) accounts for ~15 g (~1 $mg \cdot kg^{-1} \cdot min^{-1}$) or 22% of the total glucose load [58]; (4) basal HGP declined by 53%. Remarkably similar percentages have been reported for splanchnic glucose uptake (24–29%) and suppression of HGP (50–60%) in normal subjects by all other investigators [44, 52, 59–61]. Four studies [51, 59–61] have examined the contribution of skeletal muscle to the disposal of oral glucose and the results have varied from a low of 26% of the ingested glucose load [59] to a high of 56% [61], with a mean of 45%. These results emphasize several important differences between oral vs i.v. glucose administration. Following glucose ingestion: (1) HGP is less completely suppressed; (2) peripheral tissue (primarily muscle) glucose uptake is quantitatively less

Table 1. Balance sheet for the disposition of an oral glucose load in normal subjects. Summarized from reference 57

Glucose	Mean ± SEM (g)	Range (g)
A. Ingested	68 ± 3	55 – 93
B. Appearing in peripheral plasma (oral)	50 ± 4	32 – 56
C. Released by the liver	15 ± 2	5 – 20
D. Taken up by splanchnic tissues	19 ± 4	0.7 – 34
E. Taken up by peripheral tissues	48 ± 6	28 – 83
F. Remaining in the glucose space	2 ± 2	– 2 – + 15
G. Unrecovered	18 ± 3	8 – 31
H. "Saved" by the liver	18 ± 2	12 – 26
True net splanchnic balance (D – C)	4 ± 3	– 17 – + 17
Splanchnic "conservation" (D + H)	37 ± 4	20 – 62
Splanchnic overall contribution to glucose homeostasis (D + H – C)	22 ± 4	1 – 42

Table 2. Summary of glucose metabolism following glucose ingestion in Type 2 (non-insulin-dependent) diabetic patients. The number of arrows indicates the magnitude of change

Author	Ref.	Test	Body weight	Insulin response[a]	Splanchnic glucose uptake	Suppression of HGP	Tissue Rd	Incremental tissue Rd	Glucose clearance	Forearm glucose uptake	Incremental forearm glucose uptake
Ferrannini	62	OGTT	normal weight	sl↓	N	↓	↓↓	↓↓	↓↓	–	–
Firth	44	OGTT	Obese	↓	sl↓	↓↓	↑	↓↓	↓↓	N	sl↓
Mitrakou	52	OGTT	Obese	N, delayed	sl↓	↓↓	N	↓	↓↓	N	↓
Firth	64	MM	Obese	N	sl↓	↓↓	sl↑	↓↓	↓↓	N	↓
McMahon	63	MM	Obese	↓	↑↑	↓↓	↑	↓↓	↓↓	↑	↓

[a] In all studies the plasma insulin response was deficient when viewed relative to the plasma glucose concentration

OGTT, oral glucose tolerance test; MM, mixed meal; N, normal; sl, slight; HGP, hepatic glucose production; Rd, glucose disposal

important; (3) splanchnic glucose uptake is quantitatively much more significant.

Five studies have examined the disposition of an oral glucose load in Type 2 diabetes [44, 52, 62–64] and all have revealed very similar results (Table 2). As originally demonstrated by Ferrannini et al. [62], the disturbance in glucose metabolism in Type 2 diabetic patients is accounted for by two factors: (1) decreased tissue glucose uptake (44 vs 60 over 3.5 h), (2) impaired suppression of HGP (17 vs 10 over 3.5 h). Splanchnic glucose uptake was similar in diabetic and control groups. Thus, inappropriate suppression of HGP (79 over 3.5 h) accounts for approximately one-third of the defect in total body glucose homeostasis, while reduced peripheral, presumably muscle, glucose uptake (14 g over 3.5 h) accounts for the remaining two-thirds. Essentially identical results have been reported by others [44, 52, 63, 64], including Gerich and colleagues [52]. It should be noted that the double tracer technique is associated with significant variability since it involves the subtraction of two large numbers (Ra of ^{3}H-glucose minus Ra of ^{14}C-glucose) to calculate suppression of HGP. Therefore, small differences in suppression of HGP between laboratories are likely to have little physiologic meaning. The inherent variability of the method, variation in patients characteristics and differences in insulin secretory response can easily explain the 10–20% differences in suppression of HGP reported by various investigators [44, 52, 62–64]. The important message is that everyone has found that suppression of HPG is impaired in Type 2 diabetes and that this defect can account for about one-third to one-half of the disturbance in whole body glucose homeostasis. Splanchnic glucose uptake has been reported to be normal [62], slightly decreased [44, 52, 64], or increased [63] and does not appear to contribute significantly to the impairment in oral glucose tolerance.

Special comment is warranted concerning whole body tissue glucose disposal following glucose ingestion. In absolute terms most, but not all [62], studies have shown it to be normal [52] or slightly increased [44, 63, 64] (Table 2). However, the efficiency of glucose disposal, i.e. the glucose clearance, is severely reduced. *Most importantly,* it is not the absolute glucose disposal rate, but rather the *increment* in glucose disposal *above baseline* which determines the *rise* in plasma glucose *above its fasting value.* In every published study [44, 52, 62–64] the *incremental response in whole body glucose uptake* was moderately to severely reduced in Type 2 diabetes (Table 2). Similar results have been reported for forearm *muscle* glucose uptake [44, 52, 63, 64] (Table 2). Thus, all published results [44, 52, 62–64], including those by Gerich and colleagues [52], are totally consistent and point out the important contribution of impaired muscle glucose disposal in Type 2 diabetes. The conclusion by Gerich [65] that muscle does not play an important role in impaired oral glucose tolerance in Type 2 diabetes stems from the failure to recognize that it is the incremental increase in muscle glucose disposal that determines the rise in plasma glucose concentration above baseline.

In summary, results of OGTT indicate that *both impaired suppression of hepatic glucose production and decreased tissue, muscle, glucose uptake* contribute approximately equally to the glucose intolerance of Type 2 diabetes. However, none of the currently available studies [44, 52, 62–64, 66] allows one to define whether the defects in hepatic and peripheral (muscle) glucose metabolism are the result of insulin resistance, diminished insulin secretion, or an impairment in the mass action effect of glucose (i.e. glucose resistance) to promote its own uptake.

Fasting hyperglycaemia in Type 2 diabetes: pancreas vs muscle vs liver

Once overt fasting hyperglycaemia (> 7.8 mmol/l = 140 mg/dl) has developed, HGP is elevated in absolute terms and correlates closely with the severity of fasting hyperglycaemia [1, 2, 4, 30, 33, 34, 36–42, 45]. These studies do not establish whether, in the earliest stages of Type 2 diabetes, fasting hyperglycaemia results from excessive HGP, decreased efficiency of tissue glucose uptake, or some combination of the two. Recently, this question has been addressed by DeFronzo et al. [7] in 77 lean Type 2 diabetic patients. In 33 diabetic patients with fasting glucose concentration 7.8 mmol/L (Fig. 3, shaded area), HGP (1.85 ± 0.03 mg · kg^{-1} · min^{-1}) was virtually identical to control subjects (1.84 ± 0.02 mg · kg^{-1} · min^{-1}). However, this "normal" basal rate of HGP was maintained at the expense of a two-fold greater fasting plasma insulin concen-

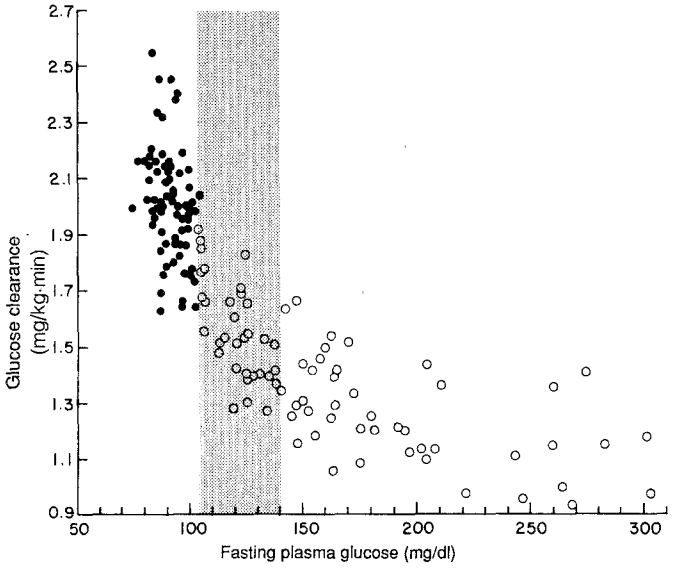

Fig. 4. Summary of the metabolic clearance rate of glucose in 77 normal weight Type 2 (non-insulin-dependent) diabetic subjects (open circles) with fasting plasma glucose concentrations ranging from 5.8 to 16.7 mmol/l (105 to 300 mg/dl). Seventy-two age- and weight-matched control subjects are shown by the open circles. In the 33 diabetic subjects with fasting plasma glucose levels less than 7.8 mmol/l (140 mg/dl) (shaded area), the glucose clearance rate fell precipitously and was inversely correlated ($r = -0.697$, $p < 0.001$) with the increase in plasma glucose levels. At fasting plasma glucose levels above 7.8 mmol/l (140 mg/dl), the rate of decline in glucose clearance began to slow and reached a plateau at glucose levels above 10 mmol/l (180 mg/dl). Reproduced from reference 1 with permission

tration (20 ± 2 vs 11 ± 1 μU/ml, $p < 0.001$) (Fig. 1). These observations are underscored by the recent reports by Eriksson et al. [21] and Gulli et al. [67] and indicate that hepatic insulin resistance is well-established early in the course of Type 2 diabetes. Only the report by Gerich [65] has suggested that HGP may be increased in patients with IGT or mild Type 2 diabetes. However, the number of patients in this study [65] is very small, patient characteristics are poorly described, the patient population is obese, treatment regimen is not defined, fasting plasma insulin concentration is not provided, and OGTT results are not given. Most importantly, in six of ten individuals with fasting glucose levels between 6–7 mmol/l (108–126 mg/dl) (see Fig. 1 of ref. 65), HGP was clearly within the normal range and the mean HGP (11.7 ± 0.3 μmol · kg^{-1} · min^{-1}) was not significantly ($t = 1.42$; $p = 0.18$; calculated from the data presented in Fig. 1 from ref. 65) elevated compared to 19 control subjects (11.2 ± 0.2 μmol · kg^{-1} · min^{-1}) with fasting glucose between 5–6 mmol/l (90–108 mg/dl). Thus, even the data of Gerich do not support his contention [65]. Moreover, the earlier publication by Gerich et al. [68] to which he refers did not examine diabetic patients with fasting glucose levels between 6–7 mmol/l. Lastly, the obesity index of the diabetic (BMI = 27.8 ± 0.6 kg/m^2) patients in the earlier Gerich's publication [68] was much greater than in the more recent article (BMI = 25.8 ± 0.8 kg/m^2), and it is obvious that the patient populations in these two papers [65, 68] were quite different. Therefore, it is not appropriate to equate the metabolic disturbances described in the earlier paper [68] with the patient population described in the more recent publication [65]. In summary neither the previous [68] nor present [65] publications justify the statement that in "individuals with fasting plasma glucose concentrations between 6 and 7 mmol/l, rates of glucose production are elevated" [65]. Rather, the data of Gerich et al. [65] demonstrate that HGP is not significantly elevated in the early stages of Type 2 diabetes. Similar results have been reported in a Type 2 diabetic primate model [14, 15].

During the postabsorptive state glucose uptake by all tissues equals HGP and, when viewed in absolute terms, is increased in Type 2 diabetes. However, since both fasting glucose and insulin concentrations are elevated, efficiency of tissue glucose uptake, i.e. glucose clearance rate, is markedly reduced early in the course of Type 2 diabetes [7] (Fig. 4). As the fasting glucose rises from 5.8 to 7.8 mmol/l (105 to 140 mg/dl), glucose clearance declines linearly ($r = 0.700$, $p < 0.001$) whereas HGP remains constant (Fig. 3). However, with fasting glucose levels above 7.8 mmol/l (140 mg/dl), the restraining effect of hyperinsulinaemia on the liver is lost and HGP increases progressively ($r = 0.847$, $p < 0.001$) (Fig. 3), while the decline in whole body glucose clearance plateaus at glucose levels between 7.8–10 mmol/l (140–180 mg/dl) (Fig. 4).

Why is fasting hyperinsulinaemia sufficient to prevent excessive HGP (Fig. 3), yet inadequate to maintain a normal basal rate of tissue glucose clearance (Fig. 4) in diabetics with fasting glucose < 7.8 mmol/L. This paradox is explained by the distinctive dose-response relationships between plasma insulin concentration vs hepatic glucose production and tissue glucose disposal [29, 33–35]. Small increments in plasma insulin (8 to 27 μU/ml) in normal subjects, suppress HGP by 68 %, but have no stimulatory effect on whole body glucose uptake [33]. Thus, in Type 2 diabetic subjects fasting hyperinsulinaemia is sufficient to offset the hepatic insulin resistance but does not stimulate tissue glucose uptake [29, 33, 69, 70], resulting in a decline in basal glucose clearance (Fig. 4).

In Type 2 diabetic subjects DeFronzo et al. [4] have shown that basal leg (muscle) glucose clearance is similar to control subjects. In contrast, Gerich et al. [68] and Firth et al. [44] have reported modestly reduced rates of glucose clearance by forearm (muscle) tissue in Type 2 diabetes in the postabsorptive state. Using hepatic vein catheterization, DeFronzo et al. have demonstrated that part of the decrease in whole body glucose clearance resides within the splanchnic tissues (liver plus gastrointestinal) [4]. However, from a purely quantitative standpoint tissues in addition to liver [4] and muscle [44, 68] must also contribute to the decline in glucose clearance. The brain represents a prime candidate to explain this decrease. In the postabsorptive state, 50–60 % of glucose disposal occurs in cerebral tissues. Brain glucose uptake is insulin-independent, saturates at plasma glucose concentrations of ~2.2 mmol/l (40 mg/dl), and remains normal in Type 2 diabetic subjects despite fasting hyperglycaemia [58]. It follows, therefore, that brain (and consequently whole body) glucose clearance *must* decline in Type 2 diabetic subjects with progressive increases in basal glucose concentration. It remains unknown whether tissues, in addition to muscle, splanchnic and brain, also contribute to the

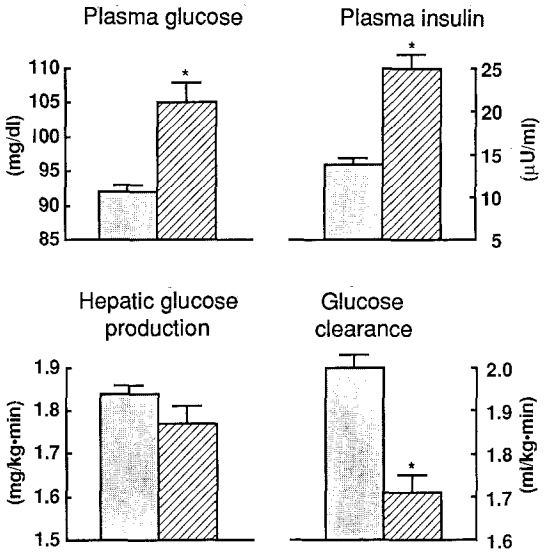

Fig. 5. Effect of overnight insulin infusion to normalize basal rate of hepatic glucose production in 19 normal weight Type 2 (non-insulin-dependent) diabetic subjects (shaded bars) and in 72 age- and weight-matched control subjects (cross-hatched bars). Despite similar rates of hepatic glucose production and a two-fold greater increase in plasma insulin concentration ($p < 0.01$), fasting plasma glucose remained significantly elevated in Type 2 diabetic patients vs control subjects. The decreased glucose clearance in Type 2 diabetic patients indicates a diminished efficiency of tissue glucose uptake. Reproduced from reference 7 with permission

decline in basal glucose clearance in Type 2 diabetic subjects.

The defects in basal HGP and tissue glucose disposal are best appreciated by studying Type 2 diabetic subjects after overnight insulin infusion to normalize basal HGP [7] (Fig. 5). Despite similar rates of HGP in control and diabetic subjects and a two-fold greater plasma insulin concentration in the latter, fasting glucose remained elevated in diabetic individuals (5.8 ± 0.2 vs 5.1 ± 0.06 mmol/l = 105 ± 3 vs 92 ± 1 mg/dl, $p < 0.01$). The persistent hyperglycaemia is explained by a decreased efficiency of tissue glucose removal (glucose clearance = 1.71 vs 2.00 $ml \cdot kg^{-1} \cdot min^{-1}$, $p < 0.01$). Further evidence for impaired tissue glucose uptake comes from studies in which Type 2 diabetic subjects received overnight insulin infusion to normalize fasting plasma glucose concentration [7] (Fig. 6). At identical plasma glucose concentrations, the *absolute* rate of tissue glucose uptake was significantly reduced in the Type 2 diabetic subjects, even though the plasma insulin concentration was more than two-fold elevated in the former group. These data unequivocally demonstrate that tissue glucose disposal is impaired in Type 2 diabetes. In contrast to the suggestion of Gerich et al. [65, 68], these results cannot be explained simply by failure of the brain to passively enhance its uptake of glucose in response to a progressive rise in fasting plasma glucose concentration.

From currently available data it is not possible to establish which defect, i.e. hepatic insulin resistance or decreased efficiency of tissue glucose removal, develops first in the evolution of fasting hyperglycaemia in Type 2 diabetes mellitus. *Three equally plausible sequences can be postulated.* First, both defects develop in parallel. As hyperglycaemia ensues (due both to excessive HGP and decreased tissue glucose uptake), basal insulin secretion is stimulated (Fig. 1). The resultant hyperinsulinaemia restores HGP to baseline, while hyperglycaemia returns tissue glucose uptake to normal. This sequence would result in normal basal rates of HGP and tissue glucose uptake but at the expense of fasting hyperglycaemia and fasting hyperinsulinaemia [1, 7]. Since the small increment in plasma insulin has no stimulatory effect on tissue glucose uptake, whole body glucose clearance falls. Second, decreased efficiency of tissue glucose uptake could represent the primary defect. As fasting plasma glucose rises, insulin secretion is enhanced; the resultant hyperglycaemia returns tissue glucose uptake to normal, while hyperinsulinaemia has two opposing actions: (1) induction of hepatic insulin resistance by down-regulating both receptor and post-receptor events [71, 72]; (2) suppression of HGP. Because these two metabolic actions of insulin offset each other, basal HGP remains unaltered. Third, hepatic insulin resistance could initiate fasting hyperglycaemia by causing a small, imperceptible rise in plasma glucose. This would stimulate insulin secretion, returning HGP to normal. Tissue glucose uptake would remain unaltered because the small rise in plasma insulin is insufficient to augment tissue glucose uptake [29, 33, 69, 70]. Consequently, tissue glucose clearance would fall. It should be noted that the statement by Gerich [65] that "for plasma glucose to increase, glucose production must exceed glucose uptake" is not, strictly speaking, correct. For plasma glucose to increase, glucose production must *transiently* exceed glucose uptake or tissue glucose uptake must *transiently* decrease below the rate of glucose production. Studies performed under steady conditions after a metabolic perturbation has occurred and the system has

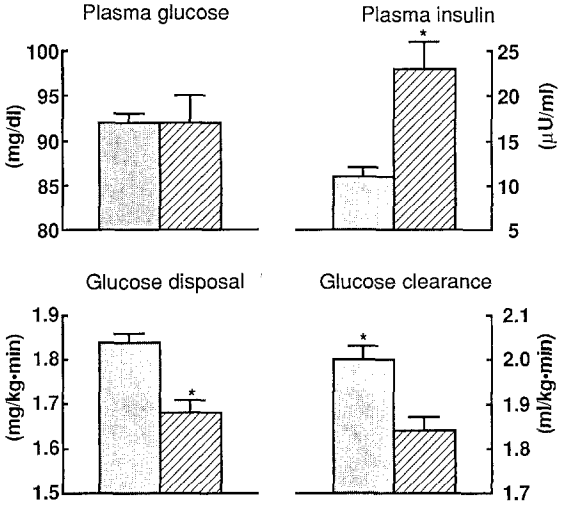

Fig. 6. Effect of overnight insulin infusion to normalize the fasting plasma glucose concentration in 11 normal weight Type 2 (non-insulin-dependent) diabetic patients (shaded bars) and in 72 age- and weight-matched control subjects (cross-hatched bars). Despite identical plasma insulin concentrations the absolute rate of whole body tissue glucose uptake in the post-absorptive state was significantly reduced in the Type 2 diabetic group ($p < 0.01$). Reproduced from reference 7 with permission

re-equilibrated *cannot* reconstruct the sequence of events that led to the establishment of the new steady state.

In summary, in Type 2 diabetic subjects with mild fasting hyperglycaemia (< 7.8 mmol/l = 140 mg/dl) *both decreased efficiency of tissue glucose uptake and hepatic insulin resistance* contribute to the elevated postabsorptive plasma glucose concentration.

Dynamic interaction between insulin action and insulin secretion in Type 2 diabetes

Type 2 diabetic subjects are characterized by both tissue (muscle and liver) insulin resistance and impaired insulin secretion. To fully appreciate the evolution of the full-blown diabetic condition, it is necessary to examine the dynamic interaction between insulin action and insulin secretion in the same individual over a wide range of insulin sensitivity. Three groups have provided such information [1, 8, 9, 12, 13, 28, 40, 41, 73]. In obesity (Fig. 2) DeFronzo, Felber and colleagues [1, 13, 41, 73] have shown that weight gain is associated with a marked reduction (40–50 %) in insulin sensitivity. Nonetheless, glucose tolerance remains normal because the Beta cell appropriately augments its insulin secretory capacity to offset the insulin resistance. Progression from normal to IGT is associated with further reduction in insulin sensitivity. However, glucose tolerance is only mildly impaired because of a further compensatory increase in insulin secretion. Onset of overt diabetes is heralded by a modest decline in insulin secretion without any additional worsening of the insulin resistance. This modest decline in insulin secretion, in the presence of severe insulin resistance, results in frank diabetes (Fig. 2). Progression from moderate to severe diabetes is associated with a further reduction in insulin secretion without any change in insulin sensitivity (Fig. 2). These observations underscore the *critical interaction* between insulin resistance and insulin secretion in the development of overt Type 2 diabetes. The sequence of events described above has been confirmed in Pima Indians [8, 9, 12], lean Caucasians [13, 34], and monkeys [14, 15].

In summary, in the earliest stage of Type 2 diabetes both hepatic and peripheral tissue resistance to insulin is well-established and is offset by the presence of compensatory hyperinsulinaemia. Overt diabetes develops only in individuals whose pancreas is unable to meet the increased and sustained demand for insulin secretion.

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References

1. DeFronzo RA (1988) Lilly Lecture. The triumvirate: beta cell, muscle, liver. A collusion responsible for NIDDM. Diabetes 37: 667–687
2. DeFronzo RA, Ferrannini E (1987) Regulation of hepatic glucose metabolism in humans. Diab Metab Rev 3: 415–459
3. DeFronzo RA, Jacot E, Jequier E, Maeder E, Wahren J, Felber JP (1981) The effect of insulin on the disposal of intravenous glucose: results from indirect calorimetry. Diabetes 30: 1000–1007
4. DeFronzo RA, Gunnarsson R, Bjorkman O, Olsson M, Wahren J (1985) Effects of insulin on peripheral and splanchnic glucose metabolism in non-insulin dependent diabetes mellitus. J Clin Invest 76: 149–155
5. Faber OK, Damsgaard EM (1984) Insulin secretion in type II diabetes. Acta Endocrinol 262 [Suppl]: 47–50
6. Faber OK, Markussen J, Naithani VK et al. (1978) Kinetics of human connecting peptide in normal and diabetic subjects. J Clin Invest 62: 197–203
7. DeFronzo RA, Ferrannini E, Simonson DC (1989) Fasting hyperglycemia in non-insulin-dependent diabetes mellitus: contributions of excessive hepatic glucose production and impaired tissue glucose uptake. Metabolism 38: 387–395
8. Saad MF, Knowler WC, Pettitt DJ, Nelson RG, Mott DM, Bennett PH (1989) Sequential changes in serum insulin concentration during development of non-insulin-dependent diabetes. Lancet I: 1356–1359
9. Lillioja S, Mott DM, Howard BV (1988) Impaired glucose tolerance as a disorder of insulin action. Longitudinal and cross-sectional studies in Pima Indians. N Engl J Med 318: 1217–1225
10. Warram JH, Martin BC, Gleason RE, Soeldner JS (1987) Slow glucose removal rate but not insulin secretion predicts development of NIDDM in offspring of two NIDDM parents. Diabetes 36 [Suppl 1]: 14 A (Abstract)
11. Yudkin JS, Alberti KGMM, McClarity DG, Swai ABM (1990) Impaired glucose tolerance-Is it a risk factor for diabetes or a diagnostic ragbag? BMJ 301: 397–401
12. Saad MF, Knowler WC, Pettitt DJ, Nelson RG, Mott DM, Bennett PH (1988) The natural history of impaired glucose tolerance in the Pima Indians. N Engl J Med 319: 1500–1505
13. Felber JP, Jallut D, Golay A, Munger R, Frascarolo P, Jequier E (1989) Obesity to diabetes. A longitudinal study of glucose metabolism in man. Diabetes 20 [Suppl 1] 221 A (Abstract)
14. Hansen BC, Bodkin NH (1986) Heterogenity of insulin responses: phases leading to Type 2 (non-insulin-dependent) diabetes mellitus in the rhesus monkey. Diabetologia 29: 713–719
15. Bodkin NL, Metzger BL, Hansen BC (1989) Hepatic glucose production and insulin sensitivity preceding diabetes in monkeys. Am J Physiol 256: E676–E681
16. Sicree RA, Zimmet P, King HO, Coventry JO (1987) Plasma insulin response among Nauruans. Prediction of deterioration in glucose tolerance over 6 years. Diabetes 36: 179–186
17. Haffner SM, Stern MP, Mitchell BD, Hazula HP, Patterson JK (1990) Incidence of type II diabetes in Mexican Americans predicted by fasting insulin and glucose levels, obesity, and body-fat distribution. Diabetes 39: 283–288
18. Haffner SM, Stern MP, Hazula HP, Mitchell BD, Patterson JK (1988) Increased insulin concentrations in non-diabetic offspring of diabetic parents. N Engl J Med 319: 1297–1301
19. Balkau B, King H, Zimmet P, Raper LR (1985) Factors associated with the development of diabetes in the Micronesian population of Nauru. Am J Epidemiol 122: 594–605
20. Boyko EJ, Keane EM, Marshall JA, Hamman RF (1991) Higher insulin and C-peptide concentrations in Hispanic population at high risk for NIDDM. San Luis Valley Diabetes Study. Diabetes 40: 509–515
21. Eriksson J, Franssila-Kallunki A, Ekstrand A et al. (1989) Early metabolic defects in persons at increased risk for non-insulin-dependent diabetes mellitus. N Engl J Med 321: 337–343
22. Ho LT, Chang ZY, Wang JT et al. (1990) Insulin insensitivity in offspring of parents with type 2 diabetes mellitus. Diab Med 7: 31–34
23. Westermark P, Wilander E (1978) The influence of amyloid deposits on the islet volume in maturity-onset diabetes mellitus. Diabetologia 15: 417–421
24. Stefan Y, Orci L, Malaisse-Lagae F, Perrelet A, Patel Y, Unger R (1982) Quantitation of endocrine cell content in the pancreas of non-diabetic and diabetic humans. Diabetes 31: 694–700

25. Steiner DF, Tager HS, Chan SJ, Nanjo T, Sanke T, Rubenstein AH (1990) Lessons learned from molecular biology of insulin-gene mutations. Diab Care 13: 600–607
26. Rossetti L, Giaccari A, DeFronzo RA (1990) Glucose toxicity. Diab Care: 13: 610–630
27. Leahy JL (1990) Natural history of beta cell dysfunction in non-insulin-dependent diabetes mellitus. Diab Care 13: 992–1010
28. Reaven GM, Hollenbeck CB, Chen YDI (1989) Relationship between glucose tolerance, insulin secretion, and insulin action in non-obese individuals with varying degrees of glucose tolerance. Diabetologia 32: 52–55
29. Bonadonna RC, Groop L, Kraemer N, Ferrannini E, Del Prato S, DeFronzo RA (1990) Obesity and insulin resistance in man. A dose response study. Metabolism 39: 452–459
30. Bogardus C, Lillioja S, Howard BV, Reaven G, Mott D (1984) Relationships between insulin secretion, insulin action, and fasting plasma glucose concentration in non-diabetic and non-insulin-dependent subjects. J Clin Invest 74: 1238–1246
31. Reaven GM, Miller R (1968) Study of the relationship between glucose and insulin responses to an oral glucose load in man. Diabetes 17: 560–569
32. Zimmet P, Whitehouse S, Alford F, Chisholm D (1978) The relationship of insulin response to a glucose stimulus over a wide range of glucose tolerance. Diabetologia 15: 23–27
33. Groop LC, Bonadonna RC, Del Prato S (1989) Glucose and free fatty acid metabolism in non-insulin dependent diabetes mellitus. Evidence for multiple sites of insulin resistance. J Clin Invest 84: 205–213
34. Firth R, Bell P, Rizza R (1987) Insulin action in non-insulin-dependent diabetes mellitus: the relationship between hepatic and extrahepatic insulin resistance and obesity. Metabolism 36: 1091–1095
35. Campbell PJ, Mandarino LJ, Gerich JE (1988) Quantification of the relative impairment in actions of insulin on hepatic glucose production and peripheral glucose uptake in non-insulin-dependent diabetes mellitus. Metabolism 37: 15–21
36. DeFronzo RA, Ferrannini E, Koivisto V (1983) New concepts in the pathogenesis and treatment of non-insulin-dependent diabetes mellitus. Am J Med 75 (1 A): 52–81
37. DeFronzo RA, Deibert D, Hendler R, Felig P (1982) Insulin sensitivity and insulin binding to monocytes in maturity-onset diabetes. J Clin Invest 63: 939–946
38. DeFronzo RA, Simonson D, Ferrannini E (1982) Hepatic and peripheral insulin resistance: a common feature in non-insulin-dependent and insulin dependent diabetes. Diabetologia 23: 313–319
39. Simonson D, Ferrannini E, Bevilacqua S et al. (1984) Mechanism of improvement in glucose metabolism following chronic glyburide therapy. Diabetes 33: 838–845
40. Golay A, DeFronzo RA, Ferrannini E et al. (1988) Oxidative and non-oxidative glucose metabolism in non-obese Type 2 (non-insulin-dependent) diabetic patients. Diabetologia 31: 585–591
41. Golay A, Felber JP, Jequier E, DeFronzo RA, Ferrannini E (1988) Metabolic basis of obesity and noninsulin-dependent diabetes mellitus. Diab Metab Rev 4: 727–747
42. Henry RR, Wallace P, Olefsky JM (1986) Effects of weight loss on mechanisms of hyperglycemia in obese non-insulin dependent diabetes mellitus. Diabetes 35: 990–998
43. Best JD, Judzewitsch RG, Pfeiffer MA, Beard JC, Halter JB, Porte D (1982) The effect of chronic sulfonyl urea therapy on hepatic glucose production in non-insulin-dependent diabetes mellitus. Diabetes 31: 333–338
44. Firth RG, Bell PM, Marsh HM, Hansen I, Rizza RA (1986) Postprandial hyperglycemia in patients with non-insulin-dependent diabetes mellitus. J Clin Invest 77: 1525–1532
45. Garvey WT, Olefsky JM, Griffin J, Hamman RF, Kolterman OG (1985) The effect of insulin treatment on insulin action in type II diabetes mellitus. Diabetes 34: 222–234
46. DeFronzo RA, Ferrannini E, Hendler R, Felig P, Wahren J (1983) Regulation of splanchnic and peripheral glucose uptake by insulin and hyperglycemia. Diabetes 32: 35–45
47. Butterfield WJH, Whichelow MJ (1965) Peripheral glucose metabolism in control subjects and diabetic patients during glucose, glucose-insulin, and insulin sensitivity tests. Diabetologia 1: 43–53
48. Revers R, Fink R, Griffin J, Olefsky J, Kolterman O (1984) Influence of hyperglycemia in insulin's in vivo effects in type II diabetes. J Clin Invest 73: 664–672
49. Kalant N, Leibovici D, Fukushima J, Ozaki S (1982) Insulin responsiveness of superficial forearm tissues in Type 2 (non-insulin-dependent) diabetes. Diabetologia 22: 239–244
50. Campbell P, Mandarino L, Gerich J (1988) Quantification of the relative impairment in actions of insulin on hepatic glucose production and peripheral glucose intake in non-insulin-dependent diabetes mellitus. Metabolism 37: 15–22
51. Jackson RA, Perry G, Rogers J, Advoni U, Pilkington TRE (1973) Relationship between the basal glucose concentration, glucose tolerance, and forearm glucose uptake in maturity onset diabetes. Diabetes 22: 751–761
52. Mitrakou A, Kelley D, Veneman T et al. (1990) Contribution of abnormal muscle and liver glucose metabolism to postprandial hyperglycemia in NIDDM. Diabetes 39: 1381–1390
53. Butterfield WJH, Whichelow MJ (1965) Peripheral glucose metabolism in control subjects and diabetic patients during glucose, glucose-insulin and insulin sensitivity tests. Diabetologia 1: 43–53
54. Zierler KL, Rabinowitz D (1963) Roles of insulin and growth hormone, based on studies of forearm metabolism in man. Medicine 42: 385–402
55. Capaldo B, Napoli R, Dimarino L, Picardi A, Riccardi G, Sacca L (1988) Quantitation of forearm glucose and free fatty acid (FFA) disposal in normal subjects and type 2 diabetic patients: evidence against an essential role for FFA in the pathogenesis of insulin resistance. J Clin Endocrinol Metab 67: 893–898
56. Marin P, Rebuffe-Scrive, Smith U, Bjorntorp P (1987) Glucose uptake in human adipose tissue. Metabolism 36: 1154-1160
57. Ferrannini E, Reichard GA, Bjorkman O et al. (1985) The disposal of an oral glucose load in normal subjects. A quantitative study. Diabetes 34: 580–588
58. Grill V (1990) A comparison of brain glucose metabolism in diabetes as measured by positron emission tomography or by arteriovenous techniques. Ann Med 22: 171–175
59. Kelley D, Mitrakou A, Marsh H et al.: Skeletal muscle glycolysis, oxidation, and storage of an oral glucose load. J Clin Invest 81: 1563–1571
60. Jackson RA, Roshania RD, Hawa MI, Sim BM, DiSilvio L (1986) Impact of glucose ingestion on hepatic and peripheral glucose metabolism in man: an analysis based on simultaneous use of the forearm and double isotope techniques. J Clin Endocrinol Metab 63: 541–549
61. Katz LD, Glickman MG, Rapoport S, Ferrannini E, DeFronzo RA (1983) Splanchnic and peripheral disposal of oral glucose in man. Diabetes 32: 675–679
62. Ferrannini E, Simonson DC, Katz LD et al. (1988) The disposal of an oral glucose load in patients with non-insulin dependent diabetes. Metabolism 37: 79–55
63. McMahon V, Marsh HM, Rizza RA (1989) Effects of basal insulin supplementation on disposition of mixed meal in obese patients with NIDDM. Diabetes 38: 291–303
64. Firth RG, Bell PM, Rizza RA (1986) Effects of tolazamide and exogenous insulin on insulin action in patients with non-insulin-dependent diabetes mellitus. N Engl J Med 314: 1280–1286
65. Gerich JE (1991) Is muscle the major site of insulin resistance in Type 2 (non-insulin-dependent) diabetes mellitus? Diabetologia 34: 607–610
66. Chen Y-DI, Jeng CY, Hollenbeck CB, Wu MS, Reaven GM (1988) Relationship between plasma glucose and insulin concentration, glucose production, and glucose disposal in normal subjects and patients with non-insulin-dependent diabetes. J Clin Invest 82: 21–25
67. Gulli G, Haffner S, Ferrannini E, DeFronzo RA (1990) What is inherited in NIDDM? Diabetes 39 [Suppl 1]: 116 A (Abstract)

68. Gerich JE, Mitrakou A, Kelly D et al. (1990) Contribution of impaired muscle glucose clearance to reduced postabsorptive systemic glucose clearance in NIDDM. Diabetes 39: 211–215
69. Zierler KL, Rabinowitz D (1964) Effect of very small concentrations of insulin on forearm metabolism. Persistence of its action on potassium and free fatty acids without its side effect on glucose. J Clin Invest 43: 950–962
70. Natali A, Santoro D, Palombo C, Cerri M, Ghione S, Ferrannini E (1991) Impaired insulin action on skeletal muscle metabolism in essential hypertension. Hypertension 17: 170–178
71. Marshall S, Olefsky J (1980) Effect of insulin incubation on insulin binding, glucose transport, and insulin degradation by isolated adipocytes. Evidence of hormone-induced desensitization at the receptor and post-receptor level. J Clin Invest 66: 763–772
72. Amatruda JM, Newmeyer HW, Chang CL (1982) Insulin-induced alterations in insulin binding and insulin action in primary cultures of rat hepatocytes. Diabetes 31: 145–148
73. Felber JP, Ferrannini E, Golay A (1987) Role of lipid oxidation in the pathogenesis of the insulin resistance of obesity and type II diabetes. Diabetes 36: 1341–1350

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