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Insulin Clearance in Health and Disease

Sonia M. Najjar,[1,*] Sonia Caprio,[2,*] and Amalia Gastaldelli[3,*]

[1]Department of Biomedical Sciences and the Diabetes Institute, Heritage College of Osteopathic Medicine, Ohio University, Athens, Ohio, USA; email: najjar@ohio.edu

[2]Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut, USA

[3]Cardiometabolic Risk Unit, Institute of Clinical Physiology–National Research Council, Pisa, Italy

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*These authors contributed equally to this article

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Abstract

Insulin action is impaired in type 2 diabetes. The functions of the hormone are an integrated product of insulin secretion from pancreatic β-cells and insulin clearance by receptor-mediated endocytosis and degradation, mostly in liver (hepatocytes) and, to a lower extent, in extrahepatic peripheral tissues. Substantial evidence indicates that genetic or acquired abnormalities of insulin secretion or action predispose to type 2 diabetes. In recent years, along with the discovery of the molecular foundation of receptor-mediated insulin clearance, such as through the membrane glycoprotein CEACAM1, a consensus has begun to emerge that reduction of insulin clearance contributes to the disease process. In this review, we consider the evidence suggesting a pathogenic role for reduced insulin clearance in insulin resistance, obesity, hepatic steatosis, and type 2 diabetes.

THE PHYSIOLOGY OF INSULIN CLEARANCE

Insulin regulates glucose concentrations by promoting glucose uptake and metabolism in most peripheral tissues (mainly skeletal muscle and adipose tissue) and suppresses gluconeogenesis (in the liver). In contrast, other organs, such as the brain, do not need insulin to metabolize glucose, but its action is impaired in the presence of insulin resistance (1).

Insulin is secreted by pancreatic β-cells in response to changes in glucose concentrations. Thus, when β-cells sense an increase in glucose concentrations (e.g., after a meal), insulin is released in pulses and proportionally to the change in glycemia, in part potentiated by other hormones (e.g., incretins) and nutrients (e.g., amino acids and fatty acids) (2). In contrast, when glucose concentration is reduced (e.g., during fasting), insulin secretion is decreased to basal levels to maintain life. Glucose tolerance is preserved until peripheral insulin concentrations are high enough to overcome the defect in insulin action (2, 3).

The pancreas releases pulses of insulin into the portal vein to be delivered to hepatocytes via fenestrae in the capillaries of the liver, where it is endocytosed receptor-bound and targeted to its degradation (**Figure 1**). In this manner, most of the secreted insulin is cleared (extracted) by the liver during its first pass (~60–70%). Insulin that is not extracted by the liver appears in the systemic circulation, where it is used in part by peripheral tissues and then further extracted by the liver during the second pass through the hepatic artery (**Figure 1**). Among peripheral tissues, the kidney is responsible for ~25% of endogenous insulin clearance (4) and ~30% of peripherally infused insulin (5, 6). Muscle extraction was also reported to be at ~6% (7), and the other peripheral insulin-sensitive tissues (including adipose tissue) account for the remaining ~7–14% of total

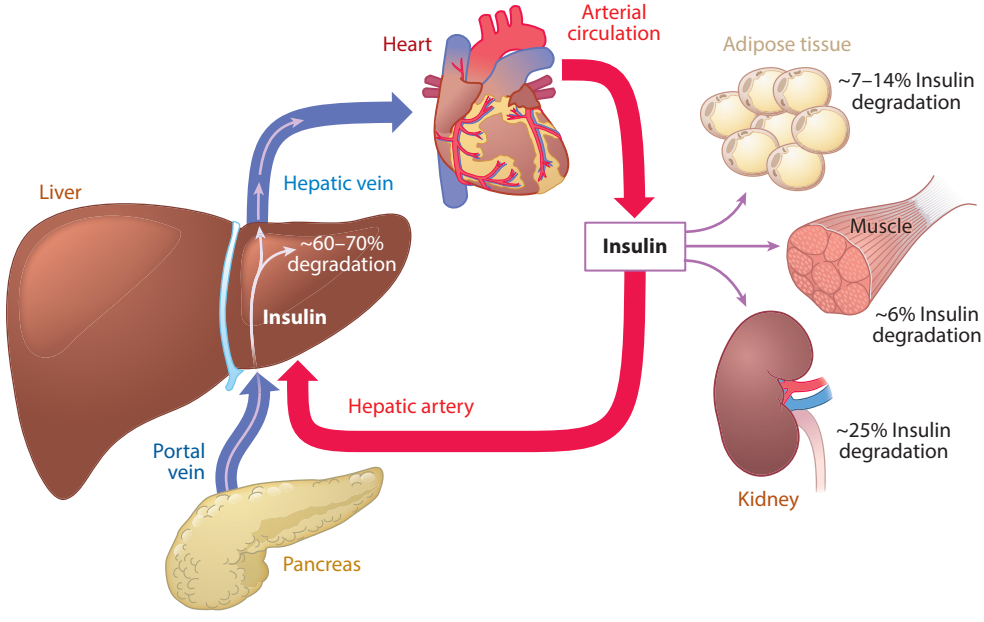

Figure 1

The journey of insulin. The pancreas releases insulin into the portal vein in a pulsatile manner to be delivered to hepatocytes. The liver is the first organ exposed to insulin secretion and where most insulin is degraded during the first pass (~60–70%). The remaining insulin appears in the systemic circulation, where it is used in part by peripheral tissues (mainly muscle, adipose tissue, and kidneys) and then further extracted by the liver during the second pass through the hepatic artery.

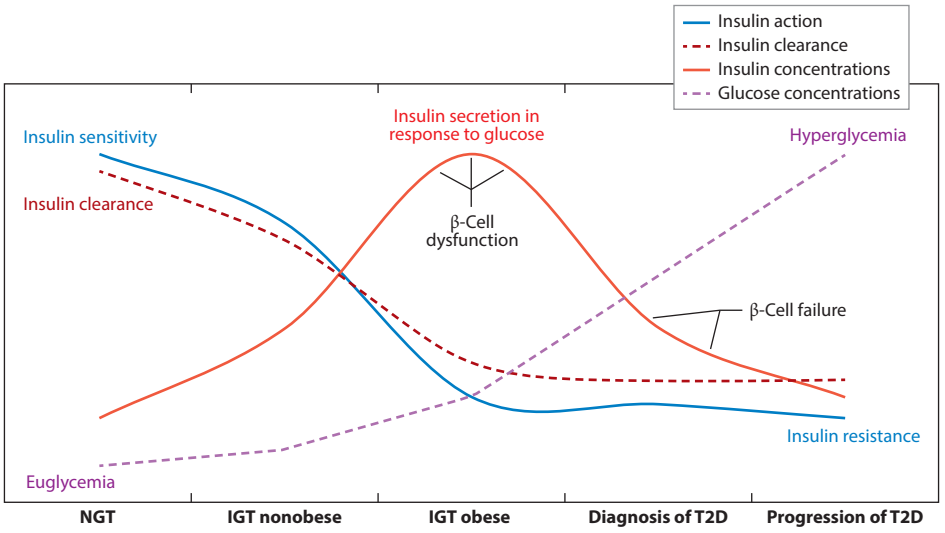

Figure 2

Natural history of T2D. The deterioration of glucose tolerance from NGT, to IGT, to T2D, and the resulting hyperglycemia are due to an imbalance between insulin secretion and tissue sensitivity to this hormone. Not all of the insulin secreted by the pancreas reaches the peripheral tissues because most of it is used and degraded by the liver soon after it is secreted. It is well established that in the progression from NGT to IGT to T2D, insulin secretion increases to overcome insulin resistance. At the same time, there is a decrease in insulin clearance (mainly hepatic), resulting in higher peripheral insulin concentrations. IGT subjects have higher insulin concentrations than NGT subjects (mainly owing to higher insulin secretion), but it is still insufficient (β-cell dysfunction) to lower both fasting and postprandial blood glucose. T2D develops when β-cells are unable to increase insulin secretion in response to increased glucose concentrations (β-cell failure) and overcome peripheral insulin resistance. Abbreviations: IGT, impaired glucose tolerant; NGT, normal glucose tolerant; T2D, type 2 diabetes. Adapted with permission from Reference 16; copyright 2019 Elsevier.

insulin clearance. In this respect, the liver acts as a modulator of insulin delivery to extrahepatic peripheral tissues.

THE INTERPLAY BETWEEN INSULIN SECRETION, CLEARANCE, AND RESISTANCE

Type 2 diabetes (T2D) is characterized by insulin resistance in insulin target tissues (skeletal muscle, liver, and adipocytes), β-cell dysfunction, and reduced insulin clearance rates (**Figure 2**) (8–16). Thus, the pancreas–liver axis plays a central role in regulating the concentration of circulating insulin, as determined by insulin secretion (from pancreatic β-cells) and clearance (by hepatocytes in the liver) (**Figure 2**). This axis is integral to the regulation of insulin action in health and disease (17).

It is now well established that in the natural history of T2D, alterations in glucose tolerance are mainly due to β-cell dysfunction, i.e., impaired insulin secretion in response to changes in glucose concentration, and secondarily to insulin resistance. This phenomenon is evident in both adults and children (3, 18–20).

Subjects with peripheral insulin resistance need higher insulin concentrations (due to the defect in insulin action), and this determines an increase in insulin secretion and a reduction in

whole-body insulin clearance (9, 21). Several studies have shown that the percentage of hepatic extraction is reduced with insulin resistance but quite stable at normal physiological insulin concentrations, consistent with insulin clearance being strictly related to insulin secretion and action (9, 12, 21).

EFFECT OF AGE ON INSULIN CLEARANCE

Insulin sensitivity and secretion are quite variable across age groups. Decreasing insulin sensitivity during pubertal maturation is an important physiological phenomenon across species (22–28). In humans, using hyperinsulinemic-euglycemic clamp analysis in a cross-sectional study, Amiel et al. (22) first described the development of insulin resistance at puberty. Similarly, Moran et al. (29) confirmed the transient fall in insulin sensitivity using hyperinsulinemic-euglycemic clamps in a large nonobese group of boys and girls at puberty. The decline in insulin sensitivity was found to be compensated for by increased insulin secretion, as documented by hyperglycemic clamp analysis in prepubertal, pubertal, and postpubertal subjects (25).

Few longitudinal studies have focused on deciphering the effect of in vivo insulin sensitivity with detailed and accurate measurements of an insulin effect on changes in sensitive fuels during the transition from prepuberty to puberty (30–32). In a very small group of prepubertal subjects with healthy weight, followed longitudinally during the progression to puberty, Hannon et al. (33) found that puberty-induced changes in insulin-stimulated fuel metabolism include reduction in peripheral glucose uptake. In oxidative and nonoxidative glucose metabolism, changes include decreased adiponectin levels but spared hepatic insulin sensitivity. The preserved effect of insulin on hepatic glucose production was also found during puberty in a cross-sectional study (23). In humans, the pubertal decline in insulin sensitivity and compensatory increase in insulin secretion have been attributed to increased circulating levels of growth hormone, accretion of body fat, and possibly increased adrenal androgen secretion after adrenarche (34, 35).

Despite the importance of these early studies, no attention was dedicated to changes in insulin clearance in puberty. Therefore, whether insulin clearance contributes significantly to insulin resistance at puberty and whether it acts as an independent risk factor for diabetes during this critical developmental stage remain unclear.

With age, glucose tolerance progressively declines (36). However, circulating insulin levels after glucose challenge are often similar to those in younger subjects with the same degree of glucose tolerance, but insulin secretion and β-cell function were found to be not different (37), reduced (38, 39), or increased (40) compared to younger counterparts. Lower insulin concentrations were associated with reduced insulin clearance (due mainly to hepatic insulin extraction) to compensate for reduced insulin sensitivity and secretion (38, 39). Although not investigated, it is possible that this is mechanistically mediated by reduced levels of hepatic carcinoembryonic antigen–related cell adhesion molecule 1 (CEACAM1) and activity of insulin-degrading enzyme with age, as suggested by compromised insulin clearance in a mouse model of aging (41, 42). However, not all elderly subjects display a reduction in insulin clearance, as shown by Ahren & Pacini (40). In these studies, elderly subjects with normal glucose tolerance and insulin sensitivity had higher glucose and lower second-phase insulin secretion in response to the frequently sampled intravenous glucose tolerance (FSIGT) test. This was partly due to increased (not reduced) hepatic insulin extraction with no changes to fasting insulin clearance and first-phase insulin secretion (40).

METABOLIC CONTRAST BETWEEN YOUTH AND ADULTS

Insulin resistance and β-cell dysfunction in both youth and adults are early precursors of T2D (43, 44). However, the progression of dysglycemia appears to be more aggressive in youth than in adults

(45, 46). In contrast to the well-characterized pathophysiology of T2D in adults, that of youth onset is poorly understood. Studies comparing youth to adults with prediabetes or T2D showed a far more aggressive disorder in youth, based on marked differences in the severity of insulin resistance, β-cell dysfunction, and insulin clearance (46). The Restoring Insulin Secretion (RISE) study provided a unique opportunity to compare the physiologic features that underlie dysglycemia in youth and adults. RISE is the first large study that included youth and adults and applied identical, sophisticated, and quantitative methodologies, including performance of the hyperglycemic clamp with arginine and the use of central laboratory for all assays, which allowed direct comparisons of β-cell function and insulin sensitivity between youth and adults. In these studies, insulin clearance was evaluated by the fasting C-peptide-to-insulin molar ratio (46). Insulin sensitivity was lower in youth than adults ($P < 0.001$). In contrast, acute, steady-state and arginine-stimulated C-peptide and insulin response to glucose were higher in youth than adults (46). After adjusting for insulin sensitivity, β-cell response was greater while insulin clearance was lower ($P < 0.001$) in youth compared to adults. The reduced insulin clearance in youth may contribute to their peripheral hyperinsulinemia (45).

The mechanisms underlying this age difference in insulin clearance remain unclear, but several mechanisms were proposed (46). It is plausible that hepatic insulin extraction is reduced to limit the workload on β-cell function, particularly in the presence of greater insulin resistance, such as that seen during puberty (46). It is also conceivable that regulators of hepatic insulin extraction differ between youth and adults. This hypothesis remains to be tested further.

ETHNIC DIFFERENCES IN INSULIN CLEARANCE: A POTENTIAL CAUSE FOR HIGHER RATES OF TYPE 2 DIABETES IN AFRICAN AMERICANS

Several longitudinal studies performed in large cohorts of >500 subjects have identified low insulin clearance rate as an independent risk factor predicting T2D in nondiabetic Hispanics, African Americans, and Native Americans (47, 48). African Americans are at an increased risk for T2D, with an incidence per 1,000 person-years that is 2.4-fold greater in African American women and ~1.5-fold greater in men compared with their white counterparts (49). Higher fasting and stimulated insulin levels have been described particularly in African American children and adults (10, 50–53). Several studies have shown that African Americans, especially women, have higher insulin concentrations during the FSIGT test due to both increased insulin secretion (i.e., C-peptide levels) and reduced insulin clearance compared to their European white counterparts (10, 50–54). In a large cohort of subjects, Bizzotto et al. (10) have shown that insulin clearance is negatively associated with the African American or Hispanic race, female sex, and female age. However, Koh et al. (52) showed that despite African Americans exhibiting higher insulin secretion and lower insulin clearance rates during the FSIGT test, the metabolic response to glucose ingestion [the oral glucose tolerance test (OGTT)] was similar across ethnic groups. There were no significant differences in peripheral insulin concentrations, insulin secretion, and insulin clearance (which were all slightly reduced in African American versus non-Hispanic white subjects).

Using a longitudinal study design, Ball et al. (30) compared changes in insulin sensitivity and β-cell function during puberty in white versus black youth. They observed reduced insulin sensitivity during puberty followed by a rebound by the end of puberty, with a significant fall in the disposition index (DI), a marker of β-cell function, across puberty in black but not white subjects (30).

The hyperinsulinemia described in African American children has been considered as an adaptive mechanism to compensate for the lower insulin sensitivity by increased insulin secretion (55, 56). Alternatively, reduced insulin clearance described in these subjects could contribute

to hyperinsulinemia. Studies by Arslanian et al. (50) found that African American adolescents had lower C-peptide-to-insulin ratios and, hence, reduced insulin clearance. Studies from the Bogalusa Heart Study (24) showed that African American children had higher fasting insulin levels and lower C-peptide-to-insulin ratios, suggesting that their elevated fasting insulin levels likely resulted from decreased insulin clearance and not increased secretion. However, whether the higher fasting insulin level in African American children is secondary to reduced hepatic clearance, is due to induced basal insulin secretion, or is caused by a combination of increased secretion and reduced clearance remains debatable.

The question as to why insulin clearance is lower in African American children has been addressed by Piccinini et al. (57) by employing a novel modeling approach based on measurements of insulin and C-peptide collected during the FSIGT tests to estimate hepatic versus extrahepatic insulin clearance rates. These studies were conducted on a multiethnic cohort of 203 nonobese boys and girls at 7–13 years of age. The results demonstrated that hepatic insulin clearance is 74% lower in African American than in European African children. Despite the importance of this study, these results do not explain causality. Both genetic and lifestyle differences likely contribute to these significant ethnic differences in hepatic insulin clearance. It should also be noted that no information regarding the intrahepatic fat content, a known modulator of hepatic insulin clearance, was obtained.

LOWER INSULIN CLEARANCE: IS IT DUE TO SATURABILITY?

It is not established whether the decrease in insulin clearance observed after a glucose load is simply an adaptation to the need for more insulin in the periphery (9) or whether it is due to a saturation of hepatic insulin receptors, as recently suggested (58, 59). Insulin clearance is determined by the rate of receptor-mediated insulin endocytosis (41, 60) and, for this reason, it is likely to be a saturable process.

Polidori et al. (11) have recently proposed a model for estimating hepatic and extrahepatic insulin clearance in humans. The model predicted saturability of hepatic extraction at relatively low peripheral insulin concentrations, whereas previous data indicate that hepatic insulin extraction does not reach saturability until the prehepatic insulin concentrations rise into supraphysiologic range (5, 61–63). Comparing intraportal versus peripheral insulin infusion in dogs, Edgerton et al. (63) have shown a high liver-to-periphery-insulin ratio (with portal concentrations up to 400 pmol/L) in association with higher hepatic extraction in absolute, but not relative, terms. Using insulin clamps in combination with renal vein catheterizations to evaluate hepatic insulin extraction, Ferrannini et al. (5) showed that hepatic extraction is constant up to a plasma insulin concentration of ~500 μU/mL. Therefore, even though obese nondiabetic subjects may display a markedly higher insulin secretion after a glucose load, it is unlikely that insulin concentration in their portal vein exceeds 500 μU/mL (5). Thus, factors other than hepatic insulin saturability must explain the decrease in hepatic insulin clearance following glucose ingestion.

Moreover, in insulin-resistant states, insulin clearance is rapidly reduced as soon as insulin secretion increases, but it remains reduced even when insulin secretion rates return close to fasting levels (9). This indicates that saturation of receptors is not the only explanation for reduction in insulin clearance. Instead, it points toward a mechanism against β-cell stress in the postprandial state (by reducing hepatic insulin clearance), while preventing hypoglycemic events during fasting conditions.

Most of the results of saturation of hepatic insulin clearance are derived from the model of Polidori et al. (11). In the modeling analysis, only hepatic extraction was considered saturable, whereas constant fractional insulin extraction was assumed for extrahepatic tissues (i.e., insulin extraction was predicted to be linear) (11). We cannot exclude that peripheral extraction is limited

by insulin receptors, as suggested by the decline in the extraction fraction and clearance of insulin in skeletal muscle during a 2-h hyperinsulinemic-euglycemic clamp (1 mU/kg/min), indicating saturability of muscle insulin uptake at physiological hyperinsulinemia (64). Thus, not only hepatic but also extrahepatic extraction may account for a reduction in insulin clearance due to saturation.

LOWER INSULIN CLEARANCE IN OBESITY AND NONALCOHOLIC FATTY LIVER DISEASE

Several studies in humans and animal models have provided convincing evidence that impaired hepatic insulin clearance is a major cause of hyperinsulinemia in obesity (14, 65–70). Reduced insulin clearance has been described in obese adults and youth with insulin resistance (59, 71), even in the absence of dysglycemia. In animal models, reduction in hepatic insulin clearance has been proposed as an early homeostatic mechanism to preserve β-cell function in the context of increased insulin resistance (72).

In a recent study, our group, led by Galderisi (71), examined changes in insulin clearance in young individuals with different levels of glucose tolerance and insulin sensitivity. Sera insulin and C-peptide concentrations were simultaneously measured during hyperinsulinemic-euglycemic and hyperglycemic clamps, and a model-based method was used to assess insulin clearance. This allowed for not only the estimation of several parameters of insulin clearance, but also the determination of its effect on β-cell function (71). The study enrolled 110 participants who had a baseline OGTT together with hyperglycemic and hyperinsulinemic-euglycemic clamp analyses followed by a second OGTT two years later (71). Based on the insulin sensitivity measured during the hyperinsulinemic-euglycemic clamp, subjects were stratified into four groups: 43 Ob-NGT-IS (obese-normal glucose tolerant-insulin sensitive), 43 Ob-NGT-IR (obese-normal glucose tolerant-insulin resistant), 14 Ob-IGT (obese-impaired glucose tolerant), and 10 lean NGT (normal glucose tolerant). Whole-body insulin clearance did not differ between lean and Ob-NGT-IS participants. In contrast, it was ∼20% lower in Ob-NGT-IR ($P < 0.001$) and Ob-IGT ($P < 0.001$) participants compared to Ob-NGT-IS participants. This difference was supported by a reduced fractional hepatic extraction in Ob-NGT-IR and Ob-IGT participants compared to the Ob-NGT-IS group ($P = 0.025$), with similar fractional hepatic extraction in the lean and Ob-NGT-IS groups (71). Extrahepatic insulin clearance was comparable among the four groups. This suggests that changes in insulin clearance could precede the overt impairment in glucose tolerance (71). Of note, we observed the longitudinal effect of baseline clearance on the oral disposition index (oDI) calculated using C-peptide at 0–30 min of the OGTT. The follow-up oDI_{cpep} was significantly influenced by the baseline hepatic but not extrahepatic insulin clearance, with a lower hepatic clearance associated with a reduction of the DI independently of the other clinical and metabolic variables (71). In youth with obesity and insulin resistance, hepatic insulin clearance appears to play a major role in the decline of β-cell function in these subjects (71). Failure to regulate the liver-insulin gate may represent a major step toward the progression to diabetes in youth (71).

In addition to obesity, nonalcoholic fatty liver disease (NAFLD) is associated with systemic and hepatic insulin resistance (73, 74) and is reported to be significantly linked to adipose tissue insulin resistance and a rise in its proinflammatory state (75, 76). Subjects with nonobesity or moderate obesity have similar insulin clearance rates in the presence of very different insulin secretion rates regardless of whether or not they are glucose tolerant. However, very high insulin concentrations are often observed in subjects with NAFLD, consistent with their more robust hepatic and peripheral insulin resistance than subjects without NAFLD, as we have recently reported (77). In this study, we could not evaluate insulin secretion or clearance because no C-peptide data were available, but we observed that the DI in subjects with normal glucose

tolerance and NAFLD or nonalcoholic steatohepatitis (NASH) was much higher than the DI in insulin-sensitive NGT subjects without NAFLD/NASH (77). This finding agrees with those of Smith et al. (21), who showed reduced fractional hepatic insulin extraction and much higher insulin concentrations during the OGTT in obese subjects with NAFLD compared to nonobese and obese subjects without NAFLD. Similarly, Kotronen et al. (78) observed lower hepatic insulin clearance in T2D Finnish patients exhibiting more hepatic steatosis with hepatic and adipose tissue insulin resistance than nondiabetic subjects, similar to our findings in T2D US patients with NAFLD (79). Bril et al. (80) showed that in subjects with biopsy-proven NASH, there was a stepwise decrease in whole-body insulin clearance as subjects progress to simple steatosis and then to NASH, whereas the presence of steatosis was associated with a decrease in hepatic insulin extraction independently of the severity of liver disease. Moreover, Matsubayashi et al. (81) have reported a stronger deleterious effect of fat deposition in the liver on hepatic insulin clearance than adiposity, per se, in T2D Japanese patients.

MECHANISMS UNDERLYING THE EFFECT OF OBESITY ON INSULIN CLEARANCE

Most T2D patients exhibit abdominal obesity (82) that is commonly associated with insulin resistance in liver and extrahepatic peripheral tissues (83–86). Obesity represents a chronic subacute inflammatory state (87–89) that is characterized by the elevated release of adipokines with adverse effects on insulin action (90–92) and reduced adiponectin production in the abdominal fat depot (93).

Abdominal obesity is also associated with elevated lipolysis-derived plasma free fatty acids (FFAs) in the portal vein (85, 94), thus forming an independent risk factor for glucose intolerance and its progression to T2D (95–98) and for NAFLD and hepatic inflammation and injury independently of obesity and T2D (75).

Mobilization of FFAs to the liver during excess energy supply causes hepatic insulin resistance and increased gluconeogenesis (portal hypothesis) (99–101) via several mechanisms. These include activation of the Jun N-terminal kinase (JNK) pathway and increasing tumor necrosis factor-alpha (TNF-α) secretion (102) in addition to promoting protein kinase C (PKC) epsilon and lambda enzymatic activities (103). High levels of circulating FFAs reduce insulin binding to its receptor and degradation in isolated rat hepatocytes (104), thus contributing to impaired hepatic insulin clearance in obesity (105). Consistently, infusion of FFAs (106) and intralipid-heparin (107) in the portal vein causes reduction in hepatic insulin removal in aged rats and normal dogs, respectively. Similarly, a rise in plasma FFAs by splanchnic intralipid-heparin infusion in adult women suppresses endogenous insulin clearance independently of glucose and without significantly affecting the insulin secretion rate (108).

However, the regulation of insulin clearance by lipolysis-derived fatty acids in obesity-associated insulin resistance in human subjects is still under debate. Results obtained early after bariatric surgery, i.e., after massive stimulation of lipolysis and fatty acid overflow, have shown increased rather than reduced insulin clearance. Bojsen-Møller et al. (109) have shown that fasting hepatic insulin clearance (measured as the fasting C-peptide-to-insulin ratio) increased at one week and lasted for 1 year post Roux-en-Y gastric bypass (RYGB) in 32 obese T2D and NGT Danish patients. Similarly, morbidly obese Austrian patients with T2D responded within a week post-RYGB with an increase in hepatic insulin clearance and loss of body weight (110). In a cohort of Italian patients, insulin clearance increased one week after RYGB or gastric banding surgery (111). This earlier improvement in hepatic insulin clearance and sensitivity is consistent with improved insulin extraction in parallel to the loss of abdominal fat in women 18–51 years of age undergoing caloric restriction (112). In contrast, Kim et al. (113) showed that the insulin clearance rate is lowered in obese subjects secondarily to insulin resistance but not to excess adiposity, per se.

Nonetheless, our studies on CEACAM1, a transmembrane glycoprotein that is highly expressed in liver, provides a novel mechanistic underpinning for the effect of obesity-associated FFAs on hepatic insulin clearance (114–116). CEACAM1 promotes the rate of receptor-mediated insulin uptake and its targeting to the degradation process in hepatocytes and renal proximal tubule cells (114, 117). Feeding wild-type mice a rich high-fat diet causes a progressive decrease in hepatic CEACAM1 transcription via an FFA-activated peroxisome proliferator-activated receptor alpha (PPARα)-mediated mechanism (118, 119). This removes the negative effect of CEACAM1 on fatty acid synthase (FASN) activity (120) to reduce malonyl-CoA levels and promote long-chain fatty acyl-CoA transport to the mitochondria for fatty acid β-oxidation (FAO) (116). When the loss of CEACAM1 reaches >60% (after ~3 weeks of high-fat intake), hepatic insulin clearance is impaired to cause chronic hyperinsulinemia, which in turn drives hepatic insulin resistance (114, 116), at least in part by downregulating insulin receptor numbers in hepatocytes (121, 122) (**Figure 3**). Hyperinsulinemia can also activate the sterol regulatory element-binding protein-1c (SREBP-1c) transcriptional activity in the liver (123) to induce lipogenic gene expression and

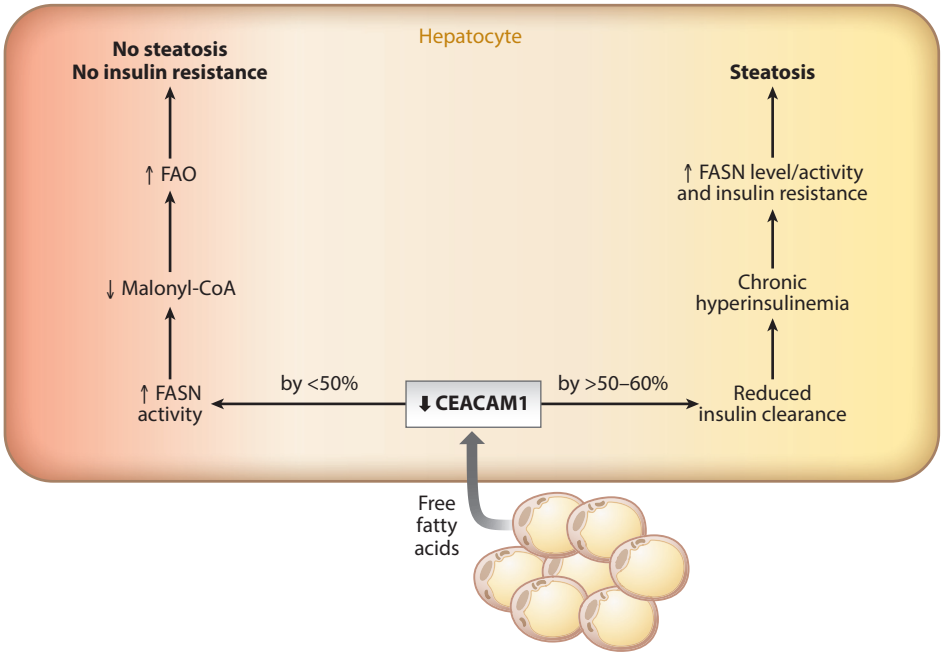

Figure 3

The effect of obesity-induced reduction of hepatic CEACAM1 levels. In response to high-fat feeding, visceral obesity develops, and the mobilization of FFAs from adipocytes to hepatocytes occurs to trigger FAO. FFAs cause a reduction of CEACAM1 expression by activating PPARα. The early reduction of CEACAM1 facilitates FAO by increasing FASN activity and producing the endogenous ligands of PPARα. Upon sustained high-fat intake for >3 weeks, CEACAM1 levels are lowered by >50–60%. This reduces hepatic insulin clearance followed by chronic hyperinsulinemia that, in turn, leads to the downregulation of insulin receptor and hepatic insulin resistance. It also activates SREBP-1c to induce the transcription of lipogenic genes and, subsequently, re-esterification. This leads to fat accumulation in hepatocytes and hepatic steatosis. It can also induce redistribution of VLDL triglycerides to adipocytes to be stored, providing a positive feedback mechanism on visceral obesity. Abbreviations: CEACAM1, carcinoembryonic antigen–related cell adhesion molecule 1; FAO, fatty acid β-oxidation; FASN, fatty acid synthase; FFA, free fatty acid; PPARα, peroxisome proliferator-activated receptor alpha; SREBP-1c, sterol regulatory element-binding protein-1c; VLDL, very-low-density lipoprotein.

tip the balance toward re-esterification rather than β-oxidation, leading to hepatic steatosis. It also causes redistribution of very-low-density lipoprotein (VLDL) triglycerides to white adipose tissue to cause visceral adiposity (116). These diet-induced metabolic abnormalities were all prevented by forced liver-specific transgenic overexpression (114) and exclusive CEACAM1 rescue in *Ceacam1*-null mice (124) and by adenoviral-mediated redelivery of CEACAM1 (116). Collectively, the data further demonstrate a regulatory role for lipolysis-derived FFAs in diet-induced metabolic derangements in the liver.

Interestingly, vertical sleeve gastrectomy in a diet-induced mouse model was recently shown to increase hepatic insulin clearance and improve hepatic insulin sensitivity, as it increases the expression of CEACAM1 and insulin-degrading enzyme independently of weight loss (125). Thus, the regulation of CEACAM1-dependent hepatic insulin clearance by lipid metabolism along the adipocyte-hepatocyte axis appears to play a paramount role in how visceral adiposity regulates hepatic insulin clearance.

LOWER INSULIN CLEARANCE: CAUSE OR CONSEQUENCE OF INSULIN RESISTANCE AND TYPE 2 DIABETES?

Since Broh-Kahn & Mirsky (126) first proposed an association between low insulin clearance and T2D, data showing low insulin clearance rates in conditions of insulin resistance (9, 12, 59), NAFLD (12, 78, 127), and diabetes (79) have emerged. However, the cause-effect relationship between reduced insulin clearance and insulin resistance in metabolic syndrome has been a subject of intense debate. Bergman et al. (128, 129) proposed the hypothesis that reduced insulin clearance (mainly hepatic) can lead to T2D. However, this hypothesis is challenged by the observation that in subjects with T2D, fasting insulin clearance is similar to that of subjects with normal or impaired glucose tolerance, while the dynamic reduction in insulin clearance, in response to the rise in insulin concentration (i.e., during OGTT or hyperinsulinemic-euglycemic clamp analysis), is much lower than in nondiabetic subjects, thus limiting the level of insulin that reaches peripheral tissues (9, 61). In general, the controversy stems partly from the heterogeneity of the metabolic disease and also from the technical challenge to distinguish which defect initiates the tightly connected myriad of these metabolic disturbances. Thus, in light of the limited available clinical evidence supporting the notion that lower insulin clearance causes insulin resistance and T2D, it has been more widely accepted that reduced insulin clearance is simply an adaptation to the insulin resistance state.

In nondiabetic subjects, insulin resistance and glucose intolerance are associated with fasting and postprandial hyperinsulinemia. Insulin clearance is inversely related to insulin action in skeletal muscle during hyperinsulinemic-euglycemic clamp analysis ($R = -0.52, P < 0.0001$), independently of obesity (9). The decrease in insulin clearance rates in obese insulin-resistant patients relative to nonobese insulin-sensitive subjects was more pronounced during the OGTT than in the fasting state (9, 59). Subjects with normal glucose tolerance and insulin sensitivity had higher glucose and lower insulin response to different challenges [during OGTT or a meal tolerance test or by insulin infusion (during analysis by a hyperinsulinemic-euglycemic clamp or the intravenous glucose tolerance test (9, 11, 130)]. However, as subjects become more insulin resistant (**Figure 2**), their postprandial insulin clearance (in response to the OGTT or hyperinsulinemic-euglycemic clamp) progressively drops (9, 12, 16, 59). These studies show that a reduction of insulin clearance follows insulin resistance in T2D.

Mechanistically, insulin action and clearance are linked (131) since both are mediated by insulin signaling pathways: In hepatocytes, the binding of insulin to its receptor activates the tyrosine kinase of the receptor as the complex enters the cell for insulin signaling to propagate and for insulin

to be eventually delivered to its degradation compartments (132). This is tightly regulated by the pulsatility of incoming insulin in the portal vein (133). An acute rise of insulin causes rapid activation of the insulin receptor to phosphorylate the surface membrane CEACAM1 followed by its association with the insulin-receptor complex to increase its rate of endocytosis (41). We have also shown that to facilitate dissociation of insulin from its receptor (so it can undergo degradation), phosphorylated and internalized CEACAM1 binds to FASN to mediate a negative effect on its enzymatic activity (41, 120). This serves to protect the liver against the lipogenic action of the physiologically higher levels of insulin in the portal vein that drive the high expression of lipogenic genes in the liver (123). In this manner, the pulsatility of insulin release sustains insulin sensitivity and prevents fat accumulation in the liver under normal physiologic conditions. Thus, it is conceivable that when the insulin receptor in hepatocytes does not sense pulses of incoming insulin in the background of supraphysiological levels of insulin in the portal vein, insulin signaling and extraction are both blunted, causing hepatic insulin resistance and restricting hepatic insulin clearance. Altered metabolic conditions that elevate insulin levels in the portal vein and mask pulsatility include but are not limited to frequent food intake and hyperphagia, obesity (abdominal adiposity), increased insulin secretion to compensate for genetic insulin resistance, and β-cell dysfunction (134, 135).

On the other hand, some studies have proposed that hyperinsulinemia drives insulin resistance (136–138), despite their being tethered to each other (139). Mechanistically, this could be mediated at least partly by the downregulation of insulin receptors in response to chronically elevated levels of insulin (121). This alternative paradigm is supported by the systemic insulin resistance state that follows the early onset of reduced hepatic insulin clearance in mice with liver-specific deletion of the *Ceacam1* gene (140). In this mouse model, deleting *Ceacam1* in the liver reduces hepatic insulin clearance to cause chronic hyperinsulinemia at 2 months of age followed by hepatic insulin resistance at 6–7 months of age (as assessed by hyperinsulinemic-euglycemic clamp analysis) (140). This is followed by visceral obesity and systemic insulin resistance at 9 months of age in parallel to the onset of the release of adipokines and lipolysis-derived FFAs (140). In addition to increased lipogenesis in the liver and redistribution of substrates to white adipose tissue, visceral obesity also results from hyperphagia that arises following a hyperinsulinemia-driven increase in hypothalamic FASN levels and activity, which induces food intake independently of leptin (141–143). Pair-feeding experiments showed that hyperphagia contributes to the development of systemic insulin resistance (140). Thus, reduced insulin clearance in the liver of these mice causes chronic hyperinsulinemia and hyperphagia that contributes to the development of visceral obesity and systemic insulin resistance. Of note, the metabolic phenotype, including insulin resistance and hyperinsulinemia in liver-specific *Ceacam1*-null mice, is much less severe than that of the LIRKO mouse with liver-specific insulin receptor–null deletion that displays reduced insulin clearance resulting from blunted insulin signaling and severe insulin resistance (144). The milder insulin resistance in liver-specific *Ceacam1*-null mice relative to LIRKO mice is reminiscent of the milder insulin resistance and obesity observed in South Asian men relative to age-matched Caucasian counterparts (145). Fed a high-caloric Western-style diet for 5 days, a group of healthy nonobese young Asian (but not Caucasian) men exhibited a rapid reduction in insulin clearance and hepatic insulin resistance (146). When healthy nonobese Japanese men were split into two groups based on their basal insulin clearance, Kaga et al. (147) found that the group with low insulin clearance exhibited mild insulin resistance in muscle in response to a two-step hyperinsulinemic-euglycemic clamp. Collectively, this provided the impetus for Watada & Tamura (145) to propose the provocative hypothesis that South Asians and Caucasians differ by the etiologies of their insulin resistance. South Asians have impaired insulin clearance causing mild obesity and selective insulin resistance and Caucasians have obesity causing more severe insulin resistance that is compensated

for by increased insulin secretion and reduced insulin clearance. While this hypothesis remains to be tested, it is interesting to note that hepatic CEACAM1 protein levels were found to be lower in 29% of South Korean insulin-resistant obese subjects with NAFLD independent of T2D (148).

CLOSING REMARKS

Because of the inverse relationship between insulin levels and receptor-mediated insulin endocytosis and degradation, any chronic hyperinsulinemic state is bound to be a state of reduced insulin clearance. However, we have observed a reduction in insulin clearance in response to a glucose load that was similar in subjects with different degrees of glucose tolerance and insulin resistance. Because these adaptations occur within minutes of insulin exposure, determining a time course of which abnormality comes first in vivo is a tall order. Nonetheless, it is possible that genetic predisposition plays a role in determining which abnormality comes first in common forms of T2D with varying tissue-specific degrees of fat deposition and insulin resistance.

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LITERATURE CITED

1. Norton L, Shannon C, Gastaldelli A, DeFronzo RA. 2022. Insulin: the master regulator of glucose metabolism. *Metabolism* 129:155142

2. Ferrannini E, Gastaldelli A, Miyazaki Y, Matsuda M, Mari A, DeFronzo RA. 2005. β-Cell function in subjects spanning the range from normal glucose tolerance to overt diabetes: a new analysis. *J. Clin. Endocrinol. Metab.* 90:493–500
3. Gastaldelli A, Ferrannini E, Miyazaki Y, Matsuda M, DeFronzo RA. 2004. Beta-cell dysfunction and glucose intolerance: results from the San Antonio metabolism (SAM) study. *Diabetologia* 47:31–39
4. Hammerman MR. 1985. Interaction of insulin with the renal proximal tubular cell. *Am. J. Physiol.* 249:F1–11
5. Ferrannini E, Wahren J, Faber OK, Felig P, Binder C, DeFronzo RA. 1983. Splanchnic and renal metabolism of insulin in human subjects: a dose-response study. *Am. J. Physiol. Renal Physiol.* 244:E517–27
6. Rabkin R, Simon NM, Steiner S, Colwell JA. 1970. Effect of renal disease on renal uptake and excretion of insulin in man. *N. Engl. J. Med.* 282:182–87
7. Sonksen PH, McCormick JR, Egdahl RH, Soeldner JS. 1971. Distribution and binding of insulin in the dog hindlimb. *Am. J. Physiol.* 221:1672–80
8. DeFronzo RA. 2009. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes* 58:773–95
9. Gastaldelli A, Abdul Ghani M, DeFronzo RA. 2021. Adaptation of insulin clearance to metabolic demand is a key determinant of glucose tolerance. *Diabetes* 70:377–85
10. Bizzotto R, Trico D, Natali A, Gastaldelli A, Muscelli E, et al. 2021. New insights on the interactions between insulin clearance and the main glucose homeostasis mechanisms. *Diabetes Care* 44:2115–23
11. Polidori DC, Bergman RN, Chung ST, Sumner AE. 2016. Hepatic and extrahepatic insulin clearance are differentially regulated: results from a novel model-based analysis of intravenous glucose tolerance data. *Diabetes* 65:1556–64
12. Jung SH, Jung CH, Reaven GM, Kim SH. 2018. Adapting to insulin resistance in obesity: role of insulin secretion and clearance. *Diabetologia* 61:681–87
13. Ader M, Stefanovski D, Kim SP, Richey JM, Ionut V, et al. 2014. Hepatic insulin clearance is the primary determinant of insulin sensitivity in the normal dog. *Obesity* 22:1238–45
14. Polonsky KS, Given BD, Hirsch L, Shapiro ET, Tillil H, et al. 1988. Quantitative study of insulin secretion and clearance in normal and obese subjects. *J. Clin. Investig.* 81:435–41
15. Kim SH, Reaven GM. 2016. Insulin clearance: an underappreciated modulator of plasma insulin concentration. *J. Investig. Med.* 64:1162–65
16. Gastaldelli A, Cusi K. 2019. From NASH to diabetes and from diabetes to NASH: mechanisms and treatment options. *JHEP Rep.* 1:312–28
17. Pajvani UB, Accili D. 2015. The new biology of diabetes. *Diabetologia* 58:2459–68
18. Burns SF, Bacha F, Lee SJ, Tfayli H, Gungor N, Arslanian SA. 2011. Declining β-cell function relative to insulin sensitivity with escalating OGTT 2-h glucose concentrations in the nondiabetic through the diabetic range in overweight youth. *Diabetes Care* 34:2033–40
19. Ferrannini E, Natali A, Muscelli E, Nilsson PM, Golay A, et al. 2011. Natural history and physiological determinants of changes in glucose tolerance in a non-diabetic population: the RISC Study. *Diabetologia* 54:1507–16
20. Stancakova A, Javorsky M, Kuulasmaa T, Haffner SM, Kuusisto J, Laakso M. 2009. Changes in insulin sensitivity and insulin release in relation to glycemia and glucose tolerance in 6,414 Finnish men. *Diabetes* 58:1212–21
21. Smith GI, Polidori DC, Yoshino M, Kearney ML, Patterson BW, et al. 2020. Influence of adiposity, insulin resistance, and intrahepatic triglyceride content on insulin kinetics. *J. Clin. Investig.* 130:3305–14
22. Amiel SA, Sherwin RS, Simonson DC, Lauritano AA, Tamborlane WV. 1986. Impaired insulin action in puberty. A contributing factor to poor glycemic control in adolescents with diabetes. *N. Engl. J. Med.* 315:215–19
23. Amiel SA, Caprio S, Sherwin RS, Plewe G, Haymond MW, Tamborlane WV. 1991. Insulin resistance of puberty: a defect restricted to peripheral glucose metabolism. *J. Clin. Endocrinol. Metab.* 72:277–82
24. Burke GL, Webber LS, Srinivasan SR, Radhakrishnamurthy B, Freedman DS, Berenson GS. 1986. Fasting plasma glucose and insulin levels and their relationship to cardiovascular risk factors in children: Bogalusa Heart Study. *Metabolism* 35:441–46

25. Caprio S, Plewe G, Diamond MP, Simonson DC, Boulware SD, et al. 1989. Increased insulin secretion in puberty: a compensatory response to reductions in insulin sensitivity. *J. Pediatr.* 114:963–67
26. Arslanian SA, Kalhan SC. 1994. Correlations between fatty acid and glucose metabolism. Potential explanation of insulin resistance of puberty. *Diabetes* 43:908–14
27. Bracho-Romero E, Reaven GM. 1977. Effect of age and weight on plasma glucose and insulin responses in the rat. *J. Am. Geriatr. Soc.* 25:299–302
28. Gatford KL, De Blasio MJ, Thavaneswaran P, Robinson JS, McMillen IC, Owens JA. 2004. Postnatal ontogeny of glucose homeostasis and insulin action in sheep. *Am. J. Physiol. Endocrinol. Metab.* 286:E1050–59
29. Moran A, Jacobs DR Jr., Steinberger J, Hong CP, Prineas R, et al. 1999. Insulin resistance during puberty: results from clamp studies in 357 children. *Diabetes* 48:2039–44
30. Ball GD, Huang TT, Gower BA, Cruz ML, Shaibi GQ, et al. 2006. Longitudinal changes in insulin sensitivity, insulin secretion, and β-cell function during puberty. *J. Pediatr.* 148:16–22
31. Goran MI, Gower BA. 2001. Longitudinal study on pubertal insulin resistance. *Diabetes* 50:2444–50
32. Hoffman RP, Vicini P, Sivitz WI, Cobelli C. 2000. Pubertal adolescent male-female differences in insulin sensitivity and glucose effectiveness determined by the one compartment minimal model. *Pediatr. Res.* 48:384–88
33. Hannon TS, Janosky J, Arslanian SA. 2006. Longitudinal study of physiologic insulin resistance and metabolic changes of puberty. *Pediatr. Res.* 60:759–63
34. Miller JD, Tannenbaum GS, Colle E, Guyda HJ. 1982. Daytime pulsatile growth hormone secretion during childhood and adolescence. *J. Clin. Endocrinol. Metab.* 55:989–94
35. Kirkman MS, Briscoe VJ, Clark N, Florez H, Haas LB, et al. 2012. Diabetes in older adults. *Diabetes Care* 35:2650–64
36. Bellary S, Kyrou I, Brown JE, Bailey CJ. 2021. Type 2 diabetes mellitus in older adults: clinical considerations and management. *Nat. Rev. Endocrinol.* 17:534–48
37. de Jesus Garduno-Garcia J, Gastaldelli A, DeFronzo RA, Lertwattanarak R, Holst JJ, Musi N. 2018. Older subjects with β-cell dysfunction have an accentuated incretin release. *J. Clin. Endocrinol. Metab.* 103:2613–19
38. Finucane FM, Sharp SJ, Hatunic M, Sleigh A, De Lucia Rolfe E, et al. 2014. Liver fat accumulation is associated with reduced hepatic insulin extraction and beta cell dysfunction in healthy older individuals. *Diabetol. Metab. Syndr.* 6:43
39. Pacini G, Beccaro F, Valerio A, Nosadini R, Crepaldi G. 1990. Reduced beta-cell secretion and insulin hepatic extraction in healthy elderly subjects. *J. Am. Geriatr. Soc.* 38:1283–89
40. Ahren B, Pacini G. 1998. Age-related reduction in glucose elimination is accompanied by reduced glucose effectiveness and increased hepatic insulin extraction in man. *J. Clin. Endocrinol. Metab.* 83:3350–56
41. Najjar SM, Perdomo G. 2019. Hepatic insulin clearance: mechanism and physiology. *Physiology* 34:198–215
42. Marmentini C, Soares GM, Bronczek GA, Piovan S, Mareze-Costa CE, et al. 2021. Aging reduces insulin clearance in mice. *Front. Endocrinol.* 12:679492
43. Jensen CC, Cnop M, Hull RL, Fujimoto WY, Kahn SE. 2002. β-Cell function is a major contributor to oral glucose tolerance in high-risk relatives of four ethnic groups in the U.S. *Diabetes* 51:2170–78
44. Weiss R, Caprio S, Trombetta M, Taksali SE, Tamborlane WV, Bonadonna R. 2005. β-Cell function across the spectrum of glucose tolerance in obese youth. *Diabetes* 54:1735–43
45. Group TS. 2013. Effects of metformin, metformin plus rosiglitazone, and metformin plus lifestyle on insulin sensitivity and beta-cell function in TODAY. *Diabetes Care* 36:1749–57
46. RISE Consortium. 2018. Metabolic contrasts between youth and adults with impaired glucose tolerance or recently diagnosed type 2 diabetes: II. Observations using the oral glucose tolerance test. *Diabetes Care* 41:1707–16
47. Lee CC, Haffner SM, Wagenknecht LE, Lorenzo C, Norris JM, et al. 2013. Insulin clearance and the incidence of type 2 diabetes in Hispanics and African Americans: the IRAS Family Study. *Diabetes Care* 36:901–7

48. Shah MH, Piaggi P, Looker HC, Paddock E, Krakoff J, Chang DC. 2021. Lower insulin clearance is associated with increased risk of type 2 diabetes in Native Americans. *Diabetologia* 64:914–22
49. Brancati FL, Kao WH, Folsom AR, Watson RL, Szklo M. 2000. Incident type 2 diabetes mellitus in African American and white adults: the Atherosclerosis Risk in Communities Study. *JAMA* 283:2253–59
50. Arslanian SA, Saad R, Lewy V, Danadian K, Janosky J. 2002. Hyperinsulinemia in African-American children: decreased insulin clearance and increased insulin secretion and its relationship to insulin sensitivity. *Diabetes* 51:3014–19
51. Chandler-Laney PC, Phadke RP, Granger WM, Munoz JA, Man CD, et al. 2010. Adiposity and β-cell function: relationships differ with ethnicity and age. *Obesity* 18:2086–92
52. Koh HE, Patterson BW, Reeds DN, Mittendorfer B. 2022. Insulin sensitivity and kinetics in African American and White people with obesity: Insights from different study protocols. *Obesity* 30:655–65
53. Piccinini F, Polidori DC, Gower BA, Bergman RN. 2017. Hepatic but not extrahepatic insulin clearance is lower in African American than in European American women. *Diabetes* 66:2564–70
54. Hasson BR, Apovian C, Istfan N. 2015. Racial/ethnic differences in insulin resistance and beta cell function: relationship to racial disparities in type 2 diabetes among African Americans versus Caucasians. *Curr. Obes. Rep.* 4:241–49
55. Gower BA, Granger WM, Franklin F, Shewchuk RM, Goran MI. 2002. Contribution of insulin secretion and clearance to glucose-induced insulin concentration in African-American and Caucasian children. *J. Clin. Endocrinol. Metab.* 87:2218–24
56. Marwitz SE, Gaines MV, Brady SM, Mi SJ, Broadney MM, et al. 2020. Cross-sectional and longitudinal examination of insulin sensitivity and secretion across puberty among non-Hispanic Black and White children. *Endocrinol. Metab.* 35:847–57
57. Piccinini F, Polidori DC, Gower BA, Fernandez JR, Bergman RN. 2018. Dissection of hepatic versus extra-hepatic insulin clearance: ethnic differences in childhood. *Diabetes Obes. Metab.* 20:2869–75
58. Piccinini F, Bergman RN. 2020. The measurement of insulin clearance. *Diabetes Care* 43:2296–302
59. Mittendorfer B, Patterson BW, Smith GI, Yoshino M, Klein S. 2022. β cell function and plasma insulin clearance in people with obesity and different glycemic status. *J. Clin. Investig.* 132:e154068
60. Meijer RI, Barrett EJ. 2021. The insulin receptor mediates insulin's early plasma clearance by liver, muscle, and kidney. *Biomedicines* 9:37
61. Gastaldelli A, DeFronzo RA, Salehi M. 2021. Comment on Piccinini and Bergman. The measurement of insulin clearance. *Diabetes Care* 2020;43:2296–2302. *Diabetes Care* 44:e98–99
62. DeFronzo RA. 1997. Pathogenesis of type 2 diabetes: Metabolic and molecular implications for identifying diabetes genes. *Diabetes Rev.* 5:177–269
63. Edgerton DS, Scott M, Farmer B, Williams PE, Madsen P, et al. 2019. Targeting insulin to the liver corrects defects in glucose metabolism caused by peripheral insulin delivery. *JCI Insight* 5:e126974
64. Eggleston EM, Jahn LA, Barrett EJ. 2007. Hyperinsulinemia rapidly increases human muscle microvascular perfusion but fails to increase muscle insulin clearance: evidence that a saturable process mediates muscle insulin uptake. *Diabetes* 56:2958–63
65. Peiris AN, Mueller RA, Smith GA, Struve MF, Kissebah AH. 1986. Splanchnic insulin metabolism in obesity. Influence of body fat distribution. *J. Clin. Investig.* 78:1648–57
66. Hansen BC, Striffler JS, Bodkin NL. 1993. Decreased hepatic insulin extraction precedes overt noninsulin dependent (Type II) diabetes in obese monkeys. *Obes. Res.* 1:252–60
67. Escobar O, Mizuma H, Sothern MS, Blecker U, Udall JN Jr., et al. 1999. Hepatic insulin clearance increases after weight loss in obese children and adolescents. *Am. J. Med. Sci.* 317:282–86
68. Rossell R, Gomis R, Casamitjana R, Segura R, Vilardell E, Rivera F. 1983. Reduced hepatic insulin extraction in obesity: relationship with plasma insulin levels. *J. Clin. Endocrinol. Metab.* 56:608–11
69. Bonora E, Zavaroni I, Coscelli C, Butturini U. 1983. Decreased hepatic insulin extraction in subjects with mild glucose intolerance. *Metabolism* 32:438–46
70. Giugliano D, Quatraro A, Minei A, De Rosa N, Coppola L, D'Onofrio F. 1993. Hyperinsulinemia in hypertension: increased secretion, reduced clearance or both? *J. Endocrinol. Investig.* 16:315–21
71. Galderisi A, Polidori D, Weiss R, Giannini C, Pierpont B, et al. 2019. Lower insulin clearance parallels a reduced insulin sensitivity in obese youths and is associated with a decline in β-cell function over time. *Diabetes* 68:2074–84

72. Kim SP, Ellmerer M, Kirkman EL, Bergman RN. 2007. β-Cell "rest" accompanies reduced first-pass hepatic insulin extraction in the insulin-resistant, fat-fed canine model. *Am. J. Physiol. Endocrinol. Metab.* 292:E1581–89
73. Zarghamravanbakhsh P, Frenkel M, Poretsky L. 2021. Metabolic causes and consequences of nonalcoholic fatty liver disease (NAFLD). *Metabol. Open* 12:100149
74. Guerra S, Mocciaro G, Gastaldelli A. 2022. Adipose tissue insulin resistance and lipidome alterations as the characterizing factors of non-alcoholic steatohepatitis. *Eur. J. Clin. Investig.* 52:e13695
75. Rosso C, Kazankov K, Younes R, Esmaili S, Marietti M, et al. 2019. Crosstalk between adipose tissue insulin resistance and liver macrophages in non-alcoholic fatty liver disease. *J. Hepatol.* 71:1012–21
76. Huh JY, Saltiel AR. 2021. Roles of IκB kinases and TANK-binding kinase 1 in hepatic lipid metabolism and nonalcoholic fatty liver disease. *Exp. Mol. Med.* 53:1697–705
77. Svegliati-Baroni G, Gaggini M, Carli F, Barbieri C, Cucco M, et al. 2020. Mechanisms for increased risk of diabetes in chronic liver diseases. *Liver Int.* 40:2489–99
78. Kotronen A, Juurinen L, Tiikkainen M, Vehkavaara S, Yki-Jarvinen H. 2008. Increased liver fat, impaired insulin clearance, and hepatic and adipose tissue insulin resistance in type 2 diabetes. *Gastroenterology* 135:122–30
79. Gastaldelli A, Cusi K, Pettiti M, Hardies J, Miyazaki Y, et al. 2007. Relationship between hepatic/visceral fat and hepatic insulin resistance in nondiabetic and type 2 diabetic subjects. *Gastroenterology* 133:496–506
80. Bril F, Lomonaco R, Orsak B, Ortiz-Lopez C, Webb A, et al. 2014. Relationship between disease severity, hyperinsulinemia, and impaired insulin clearance in patients with nonalcoholic steatohepatitis. *Hepatology* 59:2178–87
81. Matsubayashi Y, Yoshida A, Suganami H, Ishiguro H, Yamamoto M, et al. 2018. Role of fatty liver in the association between obesity and reduced hepatic insulin clearance. *Diabetes Metab.* 44:135–42
82. Boden G. 2006. Fatty acid-induced inflammation and insulin resistance in skeletal muscle and liver. *Curr. Diab. Rep.* 6:177–81
83. Reaven GM. 1995. Pathophysiology of insulin resistance in human disease. *Physiol. Rev.* 75:473–86
84. Lewis GF, Carpentier A, Adeli K, Giacca A. 2002. Disordered fat storage and mobilization in the pathogenesis of insulin resistance and type 2 diabetes. *Endocr. Rev.* 23:201–29
85. Fabbrini E, Mohammed BS, Magkos F, Korenblat KM, Patterson BW, Klein S. 2008. Alterations in adipose tissue and hepatic lipid kinetics in obese men and women with nonalcoholic fatty liver disease. *Gastroenterology* 134:424–31
86. Gastaldelli A, Miyazaki Y, Pettiti M, Matsuda M, Mahankali S, et al. 2002. Metabolic effects of visceral fat accumulation in type 2 diabetes. *J. Clin. Endocrinol. Metab.* 87:5098–103
87. Chiang SH, Bazuine M, Lumeng CN, Geletka LM, Mowers J, et al. 2009. The protein kinase IKKε regulates energy balance in obese mice. *Cell* 138:961–75
88. Shi H, Kokoeva MV, Inouye K, Tzameli I, Yin H, Flier JS. 2006. TLR4 links innate immunity and fatty acid-induced insulin resistance. *J. Clin. Investig.* 116:3015–25
89. Saltiel AR, Olefsky JM. 2017. Inflammatory mechanisms linking obesity and metabolic disease. *J.Clin. Investig.* 127:1–4
90. Perreault M, Marette A. 2001. Targeted disruption of inducible nitric oxide synthase protects against obesity-linked insulin resistance in muscle. *Nat. Med.* 7:1138–43
91. Hirosumi J, Tuncman G, Chang L, Gorgun CZ, Uysal KT, et al. 2002. A central role for JNK in obesity and insulin resistance. *Nature* 420:333–36
92. Cai D, Yuan M, Frantz DF, Melendez PA, Hansen L, et al. 2005. Local and systemic insulin resistance resulting from hepatic activation of IKK-β and NF-κB. *Nat. Med.* 11:183–90
93. Berg AH, Combs TP, Du X, Brownlee M, Scherer PE. 2001. The adipocyte-secreted protein Acrp30 enhances hepatic insulin action. *Nat. Med.* 7:947–53
94. Guo Z, Hensrud DD, Johnson CM, Jensen MD. 1999. Regional postprandial fatty acid metabolism in different obesity phenotypes. *Diabetes* 48:1586–92
95. Baldeweg SE, Golay A, Natali A, Balkau B, Del Prato S, Coppack SW. 2000. Insulin resistance, lipid and fatty acid concentrations in 867 healthy Europeans. European Group for the Study of Insulin Resistance (EGIR). *Eur. J. Clin. Investig.* 30:45–52

96. Charles MA, Eschwege E, Thibult N, Claude JR, Warnet JM, et al. 1997. The role of non-esterified fatty acids in the deterioration of glucose tolerance in Caucasian subjects: results of the Paris Prospective Study. *Diabetologia* 40:1101–6
97. Knowler WC, Pettitt DJ, Saad MF, Bennett PH. 1990. Diabetes mellitus in the Pima Indians: incidence, risk factors and pathogenesis. *Diabetes Metab. Rev.* 6:1–27
98. Bergman RN, Van Citters GW, Mittelman SD, Dea MK, Hamilton-Wessler M, et al. 2001. Central role of the adipocyte in the metabolic syndrome. *J. Investig. Med.* 49:119–26
99. Kabir M, Catalano KJ, Ananthnarayan S, Kim SP, Van Citters GW, et al. 2005. Molecular evidence supporting the portal theory: a causative link between visceral adiposity and hepatic insulin resistance. *Am. J. Physiol. Endocrinol. Metab.* 288:E454–61
100. Perry RJ, Camporez JP, Kursawe R, Titchenell PM, Zhang D, et al. 2015. Hepatic acetyl CoA links adipose tissue inflammation to hepatic insulin resistance and type 2 diabetes. *Cell* 160:745–58
101. Titchenell PM, Quinn WJ, Lu M, Chu Q, Lu W, et al. 2016. Direct hepatocyte insulin signaling is required for lipogenesis but is dispensable for the suppression of glucose production. *Cell Metab.* 23:1154–66
102. Nguyen MT, Satoh H, Favelyukis S, Babendure JL, Imamura T, et al. 2005. JNK and tumor necrosis factor-α mediate free fatty acid-induced insulin resistance in 3T3-L1 adipocytes. *J. Biol. Chem.* 280:35361–71
103. Kim YB, Kotani K, Ciaraldi TP, Henry RR, Kahn BB. 2003. Insulin-stimulated protein kinase C λ/ζ activity is reduced in skeletal muscle of humans with obesity and type 2 diabetes: reversal with weight reduction. *Diabetes* 52:1935–42
104. Svedberg J, Björntorp P, Smith U, Lonnroth P. 1990. Free-fatty acid inhibition of insulin binding, degradation, and action in isolated rat hepatocytes. *Diabetes* 39:570–74
105. Mittelman SD, Van Citters GW, Kim SP, Davis DA, Dea MK, et al. 2000. Longitudinal compensation for fat-induced insulin resistance includes reduced insulin clearance and enhanced beta-cell response. *Diabetes* 49:2116–25
106. Svedberg J, Stromblad G, Wirth A, Smith U, Bjorntorp P. 1991. Fatty acids in the portal vein of the rat regulate hepatic insulin clearance. *J. Clin. Investig.* 88:2054–58
107. Wiesenthal SR, Sandhu H, McCall RH, Tchipashvili V, Yoshii H, et al. 1999. Free fatty acids impair hepatic insulin extraction in vivo. *Diabetes* 48:766–74
108. Hennes MM, Dua A, Kissebah AH. 1997. Effects of free fatty acids and glucose on splanchnic insulin dynamics. *Diabetes* 46:57–62
109. Bojsen-Møller KN, Dirksen C, Jorgensen NB, Jacobsen SH, Hansen DL, et al. 2013. Increased hepatic insulin clearance after Roux-en-Y gastric bypass. *J. Clin. Endocrinol. Metab.* 98:E1066–71
110. Rega-Kaun G, Kaun C, Jaegersberger G, Prager M, Hackl M, et al. 2020. Roux-en-Y-bariatric surgery reduces markers of metabolic syndrome in morbidly obese patients. *Obes. Surg.* 30:391–400
111. Gastaldelli A, Iaconelli A, Gaggini M, Magnone MC, Veneziani A, et al. 2016. Short-term effects of laparoscopic adjustable gastric banding versus Roux-en-Y gastric bypass. *Diabetes Care* 39:1925–31
112. Bosello O, Zamboni M, Armellini F, Zocca I, Bergamo Andreis IA, et al. 1990. Modifications of abdominal fat and hepatic insulin clearance during severe caloric restriction. *Ann. Nutr. Metab.* 34:359–65
113. Kim MK, Reaven GM, Chen YD, Kim E, Kim SH. 2015. Hyperinsulinemia in individuals with obesity: role of insulin clearance. *Obesity* 23:2430–34
114. Al-Share QY, DeAngelis AM, Lester SG, Bowman TA, Ramakrishnan SK, et al. 2015. Forced hepatic overexpression of CEACAM1 curtails diet-induced insulin resistance. *Diabetes* 64:2780–90
115. Lester SG, Russo L, Ghanem SS, Khuder SS, DeAngelis AM, et al. 2015. Hepatic CEACAM1 overexpression protects against diet-induced fibrosis and inflammation in white adipose tissue. *Front. Endocrinol.* 6:116–22
116. Russo L, Ghadieh HE, Ghanem SS, Al-Share QY, Smiley ZN, et al. 2016. Role for hepatic CEACAM1 in regulating fatty acid metabolism along the adipocyte-hepatocyte axis. *J. Lipid Res.* 57:2163–75
117. Choice CV, Howard MJ, Poy MN, Hankin MH, Najjar SM. 1998. Insulin stimulates pp120 endocytosis in cells co-expressing insulin receptors. *J. Biol. Chem.* 273:22194–200

118. Ramakrishnan SK, Khuder SS, Al-Share QY, Russo L, Abdallah SL, et al. 2016. PPARα (peroxisome proliferator-activated receptor α) activation reduces hepatic CEACAM1 protein expression to regulate fatty acid oxidation during fasting-refeeding transition. *J. Biol. Chem.* 291:8121–29
119. Ramakrishnan SK, Russo L, Ghanem SS, Patel PR, Oyarce AM, et al. 2016. Fenofibrate decreases insulin clearance and insulin secretion to maintain insulin sensitivity. *J. Biol. Chem.* 291:23915–24
120. Najjar SM, Yang Y, Fernstrom MA, Lee SJ, Deangelis AM, et al. 2005. Insulin acutely decreases hepatic fatty acid synthase activity. *Cell Metab.* 2:43–53
121. Knutson VP, Ronnett GV, Lane MD. 1983. Rapid, reversible internalization of cell surface insulin receptors. Correlation with insulin-induced down-regulation. *J. Biol. Chem.* 258:12139–42
122. Poy MN, Yang Y, Rezaei K, Fernstrom MA, Lee AD, et al. 2002. CEACAM1 regulates insulin clearance in liver. *Nat. Genet.* 30:270–76
123. Osborne TF. 2000. Sterol regulatory element-binding proteins (SREBPs): key regulators of nutritional homeostasis and insulin action. *J. Biol. Chem.* 275:32379–82
124. Helal RA, Russo L, Ghadieh HE, Muturi HT, Asalla S, et al. 2021. Regulation of hepatic fibrosis by carcinoembryonic antigen-related cell adhesion molecule 1. *Metabolism* 121:154801
125. Ben-Haroush Schyr R, Al-Kurd A, Moalem B, Permyakova A, Israeli H, et al. 2021. Sleeve gastrectomy suppresses hepatic glucose production and increases hepatic insulin clearance independent of weight loss. *Diabetes* 70:2289–98
126. Broh-Kahn RH, Mirsky IA. 1949. The inactivation of insulin by tissue extracts; the effect of fasting on the insulinase content of rat liver. *Arch. Biochem.* 20:10–14
127. Bril F, Cusi K. 2019. Letter to the Editor: "Hepatic insulin extraction in NAFLD is related to insulin resistance rather than liver fat content." *J. Clin. Endocrinol. Metab.* 104:5249–50
128. Bergman RN, Kabir M, Ader M. 2022. The physiology of insulin clearance. *Int. J. Mol. Sci.* 23:1826
129. Bergman RN, Piccinini F, Kabir M, Kolka CM, Ader M. 2019. Hypothesis: role of reduced hepatic insulin clearance in the pathogenesis of type 2 diabetes. *Diabetes* 68:1709–16
130. Marini MA, Frontoni S, Succurro E, Arturi F, Fiorentino TV, et al. 2014. Differences in insulin clearance between metabolically healthy and unhealthy obese subjects. *Acta Diabetol.* 51:257–61
131. Koh HE, Cao C, Mittendorfer B. 2022. Insulin clearance in obesity and type 2 diabetes. *Int. J. Mol. Sci.* 23:596
132. Gorden P, Carpentier JL, Freychet P, LeCam A, Orci L. 1978. Intracellular translocation of iodine-125-labeled insulin: direct demonstration in isolated hepatocytes. *Science* 200:782–85
133. Satin LS, Butler PC, Ha J, Sherman AS. 2015. Pulsatile insulin secretion, impaired glucose tolerance and type 2 diabetes. *Mol. Aspects Med.* 42:61–77
134. Campbell JE, Newgard CB. 2021. Mechanisms controlling pancreatic islet cell function in insulin secretion. *Nat. Rev. Mol. Cell. Biol.* 22:142–58
135. Janssen JAMJL. 2021. Hyperinsulinemia and its pivotal role in aging, obesity, type 2 diabetes, cardiovascular disease and cancer. *Int. J. Mol. Sci.* 22:7797
136. Corkey BE. 2012. Banting lecture 2011: Hyperinsulinemia: Cause or consequence? *Diabetes* 61:4–13
137. Pories WJ, Dohm GL. 2012. Diabetes: Have we got it all wrong? Hyperinsulinism as the culprit: surgery provides the evidence. *Diabetes Care* 35:2438–42
138. Bojsen-Møller KN, Lundsgaard AM, Madsbad S, Kiens B, Holst JJ. 2018. Hepatic insulin clearance in regulation of systemic insulin concentrations-role of carbohydrate and energy availability. *Diabetes* 67:2129–36
139. Shanik MH, Xu Y, Skrha J, Dankner R, Zick Y, Roth J. 2008. Insulin resistance and hyperinsulinemia: Is hyperinsulinemia the cart or the horse? *Diabetes Care* 31(Suppl. 2):S262–68
140. Ghadieh HE, Russo L, Muturi HT, Ghanem SS, Manaserh IH, et al. 2019. Hyperinsulinemia drives hepatic insulin resistance in male mice with liver-specific *Ceacam1* deletion independently of lipolysis. *Metabolism* 93:33–43
141. Wortman MD, Clegg DJ, D'Alessio D, Woods SC, Seeley RJ. 2003. C75 inhibits food intake by increasing CNS glucose metabolism. *Nat. Med.* 9:483–85
142. Gao S, Moran TH, Lopaschuk GD, Butler AA. 2013. Hypothalamic malonyl-CoA and the control of food intake. *Physiol. Behav.* 122:17–24

143. Chakravarthy MV, Zhu Y, Lopez M, Yin L, Wozniak DF, et al. 2007. Brain fatty acid synthase activates PPARα to maintain energy homeostasis. *J. Clin. Investig.* 117:2539–52
144. Michael MD, Kulkarni RN, Postic C, Previs SF, Shulman GI, et al. 2000. Loss of insulin signaling in hepatocytes leads to severe insulin resistance and progressive hepatic dysfunction. *Mol. Cell* 6:87–97
145. Watada H, Tamura Y. 2017. Impaired insulin clearance as a cause rather than a consequence of insulin resistance. *J. Diabetes Investig.* 8:723–25
146. Bakker LEH, van Schinkel LD, Guigas B, Streefland TCM, Jonker JT, et al. 2014. A 5-day high-fat, high-calorie diet impairs insulin sensitivity in healthy, young South Asian men but not in Caucasian men. *Diabetes* 63:248–58
147. Kaga H, Tamura Y, Takeno K, Kakehi S, Funayama T, et al. 2017. Correlates of insulin clearance in apparently healthy non-obese Japanese men. *Sci. Rep.* 7:1462
148. Lee W. 2011. The CEACAM1 expression is decreased in the liver of severely obese patients with or without diabetes. *Diagn. Pathol.* 6:40