Hyperinsulinemia: An Early Indicator of Metabolic Dysfunction

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Hyperinsulinemia is strongly associated with type 2 diabetes. Racial and ethnic minority populations are disproportionately affected by diabetes and obesity-related complications. This mini-review provides an overview of the genetic and environmental factors associated with hyperinsulinemia with a focus on racial and ethnic differences and its metabolic consequences. The data used in this narrative review were collected through research in PubMed and reference review of relevant retrieved articles. Insulin secretion and clearance are regulated processes that influence the development and progression of hyperinsulinemia. Environmental, genetic, and dietary factors are associated with hyperinsulinemia. Certain pharmacotherapies for obesity and bariatric surgery are effective at mitigating hyperinsulinemia and are associated with improved metabolic health. Hyperinsulinemia is associated with many environmental and genetic factors that interact with a wide network of hormones. Recent studies have advanced our understanding of the factors affecting insulin secretion and clearance. Further basic and translational work on hyperinsulinemia may allow for earlier and more personalized treatments for obesity and metabolic diseases.

Freeform/Key Words: diabetes, hyperinsulinemia, hypersecretion, insulin clearance

Insulin has been known to be an essential hormone since its discovery in 1921. Insulin influences almost every organ in the body, including adipose tissue, liver, muscle, and brain, as well as bone [1], kidneys [2], and vasculature [3, 4]. Insulin, somatostatin, and glucagon fluctuate in a periodic fashion in subjects without type 2 diabetes (T2D), and pulsatile insulin secretion accounts for 75% of total insulin secretion [5–7]. These fluctuations are essential because continuous delivery of IV insulin induces desensitization to insulin, whereas pulsatile insulin delivery preserves sensitivity to insulin [8–10]. Loss of pulsatile insulin secretion is an early feature in the development of T2D [11].

Insulin concentrations are regulated by a variety of mechanisms affecting insulin clearance and secretion, which are carefully coordinated through signals from the hypothalamic–pituitary–adrenal (HPA) axis, as well as the liver–pancreas axis, the entero–osseous axis, and the bone–pancreas axis [12]. Excessive insulin secretion may lead to hypoglycemia in insulinomas and noninsulinoma pancreatogenous hypoglycemia syndrome, but these conditions are uncommon compared with dysregulated hyperinsulinemia (defined as elevated

Abbreviations: AIR, acute insulin response; AUC, area under the curve; BMI, body mass index; DNL, *de novo* lipogenesis; FFA, free fatty acid; FSIVGTT, frequently sampled IV glucose test; HOMA, homeostatic model assessment; HOMA-IR, HOMA of insulin resistance; HPA, hypothalamic–pituitary–adrenal; IGT, impaired glucose tolerance; IRAS, Insulin Resistance and Atherosclerosis Study; IRAS-FS, IRAS family study; OGTT, oral glucose tolerance test; RISC, Relationship between Insulin Sensitivity and Cardiovasular Disease; SAT, subcutaneous adipose tissue; T2D, type 2 diabetes; TG, triglyceride; VAT, visceral adipose tissue.

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circulating insulin in relationship to its usual level relative to blood glucose), which does not cause hypoglycemia. Dysregulated insulin secretion and/or clearance resulting in chronically elevated insulin without hypoglycemia is common in obesity and metabolic disorders, and it is referred to herein as hyperinsulinemia. Fasting insulin rises from normal glucose tolerance to impaired glucose tolerance (IGT) to T2D [13]. In subjects with obesity but without diabetes or hypertension, hyperinsulinemia and insulin hypersecretion are more prevalent than insulin resistance [14] and hence may precede and contribute to insulin resistance. Furthermore, cohort studies have shown that different subjects with similar degrees of insulin sensitivity may exhibit a range of insulin secretion. For example, in the Relationship between Insulin Sensitivity and Cardiovasular Disease (RISC) study, individuals with insulin hypersecretion tended to be older and have higher percent fat mass, worse lipid profiles, and higher liver insulin resistance indices compared with the rest of the cohort [15]. In the RISC study, preexposure to hyperinsulinemia stimulated a greater insulin-induced secretory response independently of insulin sensitivity [16]. Hence, hyperinsulinemia is self-perpetuating and is more likely to be a primary defect rather than a compensation for insulin resistance in the general population.

There are racial and ethnic differences in insulin sensitivity and β-cell function [17], and recent research provides insights into their underlying mechanisms. Here, we discuss genetic and environmental factors associated with insulin secretion and clearance and the metabolic consequences of hyperinsulinemia (Fig. 1).

1. Methods

We searched PubMed/MEDLINE for English articles with the search terms: hyperinsulinemia, diabetes, race, and obesity. We limited our review primarily to human studies with exceptions when studies have relevance to translational research. We selected mostly recent pertinent publications but did not exclude high-impact older papers. We reviewed the references from key papers to identify additional articles.

2. Methods to Assess Hyperinsulinemia

Insulin has a similar diurnal pattern in subjects with obesity and in lean subjects but is consistently regulated at a higher concentration [18]. The 24-hour urinary c-peptide excretion is a reflection of the area under the curve (AUC) of insulin and has been shown to be

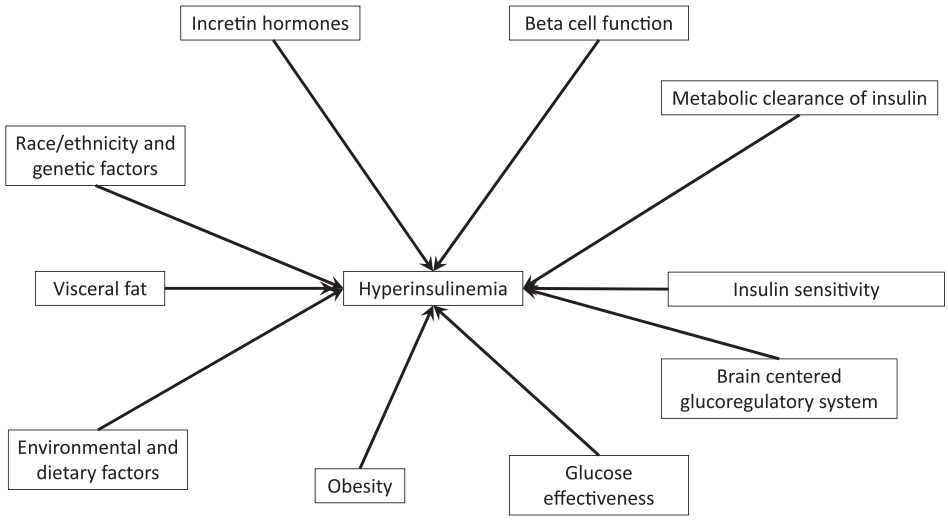

Figure 1. Diagram of multifactorial etiologies of hyperinsulinemia. Interactions between these various risk factors may also contribute to its development and progression.

negatively correlated with insulin sensitivity assessed by hyperinsulinemic-euglycemic clamp in healthy individuals [19]. Owing to logistic difficulties in obtaining repeated blood or urine samples, most studies assessed only fasting insulin. Fasting insulin has good repeatability within 4 to 8 weeks in the same subjects [20]. Hence, fasting insulin is an important metabolic parameter that is associated with the diurnal insulin exposure and insulin sensitivity and remains fairly stable over time.

Methods to assess insulin sensitivity and β-cell function include the hyperinsulinemic-euglycemic clamp, frequently sampled IV glucose test (FSIVGTT), insulinogenic index, and homeostatic model assessment (HOMA), whicheach have strengths and limitations. Hyperinsulinemic-euglycemic clamps are the gold standard to measure insulin sensitivity, but due to the logistical difficulties in performing these clamps, indices derived from an oral glucose tolerance test (OGTT) or fasting glucose and insulin are widely used. Hyperglycemic clamps provide an accurate assessment of insulin secretion capacity in response to glucose but not insulin sensitivity [21]. HOMA estimates β-cell function and insulin sensitivity based only on fasting glucose and insulin concentrations. The disposition index gives a representation of insulin secretion adjusted for insulin sensitivity.

These methods assess insulin-mediated glucose disposal, but not the ability of glucose to enhance its own disposal (independently of insulin), which is known as glucose effectiveness. Glucose effectiveness accounts for about half of overall glucose disposal, so it is relevant to hyperinsulinemia, and yet its determinants remain poorly understood [22]. Glucose effectiveness can be assessed by FSIVGTT or by pancreatic clamps, which are more difficult to perform [23].

In hyperinsulinemic-euglycemic clamp studies, whole-body insulin clearance and hepatic insulin clearance can be estimated [24]. In contrast, FSIVGTT does not differentiate between hepatic insulin clearance and whole-body insulin clearance [25, 26].

3. Causes of Hyperinsulinemia

A. Factors Associated With Hyperinsulinemia in Epidemiological Studies

A-1. Environmental factors

Diabetogenic dietary and environmental exposures may interact with hormones from the gastrointestinal tract and stimulate insulin hypersecretion under fasting conditions, leading to chronic basal hyperinsulinemia through mechanisms that remain unclear (Table 1) [27–33]. For example, air pollution has been associated with adverse lipid changes and higher fasting glucose and insulin [30] as well as higher childhood body mass index (BMI) trajectories [31]. This association has been hypothesized to be due to chronic ozone exposure and subsequent activation of the HPA axis and hormonal changes [34]. Acute bisphenol A exposure, an endocrine-disrupting chemical, at the maximal daily dose determined to be safe by the U.S. Food and Drug Administration was associated with changes in insulin and c-peptide response to an OGTT and a hyperglycemic clamp [32]. A study of Ghanaians in several countries highlighted the importance of environmental and cultural factors on insulin and glucose metabolism, BMI, insulin sensitivity, and fasting blood glucose [33].

A-2. Associations between hyperinsulinemia and race and ethnicity may be partially mediated by differences in body composition

Ethnic differences in insulin sensitivity may be underappreciated owing to the widespread use of OGTT-based surrogate measures and HOMA of insulin resistance (HOMA-IR). HOMA-IR has been validated as a marker of insulin sensitivity in European populations but showed poor correlation with insulin sensitivity assessed by FSIVGTT or clamp in Jamaican adults without diabetes [35]. A similar discrepancy was seen between OGTT-derived surrogate markers and the hyperglycemic clamp parameters in Asian Americans, blacks, whites, and

Table 1. Summary of Environmental Factors Associated With Changes in Glucose and Insulin Metabolism

Author and Citation	Primary Finding	Study Type/Design	Covariates	Limitations
Pories and Dohm 2012 [27]	Fasting insulin rises from normal glucose tolerance lean subjects to normal glucose tolerance subjects with obesity to subjects with T2D Hyperinsulinemia corrects rapidly to normal levels after bariatric surgery	Review	NA	Mechanisms for metabolic improvements following bariatric surgery remain unclear
Corkey 2012 [28]	Large numbers of environmental chemicals are detectable in food and human serum, but evidence is lacking on their effects on metabolic health	Review	NA	Further research is necessary to validate and confirm mechanisms
Corkey 2012 [29]	In cultured INS-1 cells, monooleoylglycerol, saccharin, aspartame, sucralose, and iron stimulated insulin secretion	Review	NA	Translational work is needed to validate these *in vitro* findings
Chen *et al.* 2016 [30]	Air pollution exposure is associated with increases in fasting glucose and insulin	Cohort	Socioeconomic status, age, sex, percent body fat	Residual confounding
Kim *et al.* 2018 [31]	Early life near roadway air pollution exposure is associated with greater increases in BMI and higher attained BMI at age 10 y	Cohort	Age, sex, race/ethnicity, parental education, language	Unclear mechanism Residual confounding possible
Stahlhut *et al.* 2019 [32]	Acute bisphenol A exposure is associated with an increase in disposition index	Crossover trial with OGTT and hyperglycemic clamp	NA given crossover design	Acute exposure, small sample size
Meeks *et al.* 2017 [33]	Differences in BMI and waist circumference account for a significant proportion of the geographical variation among sub-Saharan African subjects	Cross-sectional	Age, sex, family history of diabetes, anthropometrics, health-related behaviors, geographical location	Residual confounding

Abbreviation: NA, not applicable.

Mexican Americans [36]. Hence, widely used surrogate markers of insulin sensitivity and β-cell function may not be accurate in non-European populations.

The Insulin Resistance and Atherosclerosis Study (IRAS) was a multicenter cross-sectional study of insulin sensitivity assessed by FSIVGTT and cardiovascular risk factors in white, black, and Hispanic patients in the United States [37]. This study provided further insights into the genetic variations underlying the racial and ethnic differences in hyperinsulinemia and diabetes risk. Fasting insulin was higher in subjects with IGT compared with subjects with normal fasting glucose and glucose tolerance [38]. Waist circumference was positively correlated with fasting insulin in white and black patients even after adjusting for glucose tolerance [39]. A 5-year follow-up study showed that the disposition index and glucose effectiveness were independent predictors of incident T2D after adjusting for traditional risk factors [40].

The National Health and Nutrition Examination Survey also demonstrated differences between whites, Hispanics, and blacks in hyperinsulinemia and BMI. There was a significant increase in fasting insulin levels from 1988 to 1994 and 1999 to 2002, which persisted despite adjusting for BMI and waist circumference [41]. Additionally, racial disparities in the prevalence of obesity increased, with black having greater increases in BMI and waist circumference from 1988 to 2004 than did whites or Hispanics [42]. However, National Health and Nutrition Examination Survey data are cross-sectional and lack detailed metabolic assessments of insulin sensitivity and secretion.

Racial differences in hyperinsulinemia are apparent at a young age. The Bogalusa Heart Study of 377 children and adolescents who underwent an OGTT demonstrated that blacks had significantly higher insulin responses than did whites when assessed by the AUC and insulin/glucose ratios at 30 and 60 minutes [43]. These differences were consistent across Tanner stages I to V. Consistent with this, blacks had significantly higher first- and second-phase insulin secretion during a hyperglycemic clamp than did whites [44].

Racial differences in visceral and subcutaneous adipose tissue distributions in women have been reported, with blacks having less visceral fat than whites but paradoxically lower insulin sensitivity [45]. For example, in the Dallas Heart Study, blacks had less visceral fat and hepatic steatosis than did whites and Hispanics, but more insulin resistance by HOMA-IR [46]. In adolescents with obesity, despite similar total percent body fat, Hispanics had greater intramyocellular lipid deposition and blacks had lower hepatic fat accumulation compared with whites [47]. However, these differences in body composition cannot fully account for the differences in β-cell function. In women without diabetes, blacks had greater insulin secretion compared with whites across a wide range of ages, independently of adiposity and insulin sensitivity, and there were no differences in glucose effectiveness [48].

Racial differences have also been reported in the effects of visceral fat mass on serum triglycerides (TGs) and in the upper and lower body subcutaneous fat distribution in women with obesity [49]. Increased visceral adipose tissue (VAT) is associated with higher fasting insulin and insulin AUC during an OGTT, independently of subcutaneous adipose tissue (SAT), skeletal muscle mass [50], insulin resistance, and inflammation [51–55]. In IRAS, VAT and SAT accounted for 27% of the model R^2 for insulin sensitivity and 16% of the model R^2 for disposition index, adjusting for age, sex, ethnicity, and BMI [56]. VAT contributes to delivery of free fatty acids (FFAs) to the liver, which negatively affects hepatic insulin sensitivity and is associated with reduced insulin clearance [57, 58]. Insulin has an antilipolytic effect on VAT that reduces portal FFAs, and this may be a key mechanism whereby insulin regulates hepatic glucose production in addition to its direct effects on the liver [59, 60].

Central adiposity is associated with lower adiponectin, an adipokine that is normally associated with improved insulin sensitivity [61]. Adiponectin was also negatively associated with VAT, SAT, pericardial fat, and intrathoracic fat in the Framingham Heart Study [62]. There is a strong negative correlation between fasting insulin and adiponectin in whites and Pima Indians [63].

Detailed metabolic studies have shown the important contribution of hyperinsulinemia in Pima Indians, who have a remarkably high prevalence of T2D of 38% [64]. Hormonal and

metabolic studies in this population included oral and IV glucose tolerance tests along with body composition. In Pima young adults, high fasting plasma insulin and higher insulin at 30 and 120 minutes were highly heritable and were all predictors of incident T2D [65, 66]. As in IRAS, progression from normal glucose tolerance to IGT to T2D was associated with an increase in fasting insulin levels [67]. Hyperinsulinemia was seen even in Pima prepubertal girls and boys aged 6 to 7. There was no significant difference in the visceral or subcutaneous fat area at L4/L5 in a sample of Pima Indians and whites matched for percent body fat, yet the Pima had significantly higher fasting insulin and lower insulin sensitivity [68]. Hyperinsulinemia was also associated with weight gain and triceps skinfold thickness in the prepubertal years [69].

Racial and ethnic differences in pancreatic fat may account for some of these differences. Fasting and 2-hour insulin during an OGTT were lower in whites than blacks in a study that quantified VAT, pancreatic fat, and hepatic TGs in 100 subjects without T2D. VAT was highest in Hispanics and lowest in blacks [70]. Pancreatic TGs were significantly higher in whites and Hispanics than in blacks [70]. Hepatic TG levels were higher in Hispanics than in whites and blacks [70]. Blacks had the highest disposition index and acute insulin response (AIR) but lowest insulin sensitivity [70]. The effect of a one-unit increase in pancreatic TGs on AIR was largest in blacks compared with whites and Hispanics [70]. However, there was no association between pancreatic fat and β-cell function in another study of young German women [71]. These studies used different methods to estimate β-cell function, which may account for some of these discrepancies.

A systematic review and meta-analysis of studies that measured insulin sensitivity and AIR by the FSIVGTT in Africans, whites, and East Asians confirmed that in subjects with normal glucose tolerance, there is substantially lower insulin sensitivity and higher AIR in African cohorts compared with whites and East Asians, with some subjects exhibiting insulin hypersecretion relative to their degree of insulin sensitivity in each case [72]. Racial and ethnic differences in hyperinsulinemia, as well as glucose and lipid metabolism, are well established [73]. Hence, genetic differences may underlie some of the associations between insulin secretion, insulin resistance, and lipid stores.

A-3. Genetic and epigenetic variants associated with hyperinsulinemia act via several pathways

Genetic differences and epigenetic changes during gestation may underlie the association between *in utero* exposure to gestational diabetes and increased risk of childhood overweight and obesity [74]. Epigenetic changes in *GNAS* have also been associated with early-onset obesity [75]. Subjects who had parents with T2D had higher BMI and fasting insulin compared with those who had no family history of diabetes in the RISC study [76].

Studies have implicated several genes involved in obesity and other metabolic outcomes and hyperinsulinemia. The GUARDIAN consortium study of Mexican Americans provided strong evidence for the heritability of insulin sensitivity, AIR, and metabolic clearance of insulin [77]. Distinct clusters of genes have been shown to be associated with β-cell function, body weight, and different diabetes phenotypes [78, 79]. In IRAS, a genome-wide association study identified loci associated with insulin sensitivity and β-cell function in blacks and Hispanics [80], and candidate genes for the disposition index and AIR in blacks were identified [81]. In the IRAS Family Study (IRAS-FS), the heritability of insulin sensitivity assessed by FSIVGTT (0.310) was greater than the heritability of fasting insulin (0.171) and HOMA-IR (0.163) [82].

Genetic variants of *FTO* also influence the risk of obesity and fasting insulin [83]. Paternal transmission of a polymorphism associated with insulin gene expression conferred an 80% greater risk of early-onset obesity [84]. A genome-wide association study in Indian Asians found that a common variant near *MC4R* was associated with a higher HOMA-IR, increased waist circumference, and features of metabolic syndrome [85]. Finally, a Hispanic cohort

study identified genetic loci that regulate insulin clearance, which has a heritability of 73% [86].

Individuals with ≥17 alleles that raised fasting insulin tended to have higher TG levels, more hepatic steatosis, increased risk of T2D, coronary artery disease, and high blood pressure but a paradoxically lower BMI [87]. In contrast, a Mendelian randomization study of subjects from predominantly European ancestry found a strong association between genes associated with higher insulin concentration at 30 minutes after an OGTT and a higher BMI [88]. These discrepancies may be reconciled by the fact that fasting insulin and insulin secretion may have different genetic determinants. These genetic studies underscore that there are many etiologies for abnormalities in insulin secretion and sensitivity, and they reinforce the paradigm that relative insulin hypersecretion can be pathogenic.

B. Factors Affecting Insulin Clearance With a Focus on Race/Ethnicity

Fasting insulin levels are determined by the dynamic balance between insulin secretion, insulin sensitivity, glucose effectiveness, and insulin clearance, each of which may have different determinants [89]. Estimates of the relative importance of insulin secretion and clearance to hyperinsulinemia have varied depending on the study methodology and population, but both are likely important. One study found that 75% of the hyperinsulinemia is due to a reduction in hepatic metabolic clearance of insulin in subjects with normal fasting glucose and obesity [90]. Using different methods and a different study population, Polonsky *et al.* [91] found that hyperinsulinemia in subjects with obesity was predominantly driven by increased secretion with a minor contribution of reduced hepatic extraction of insulin. These differences may be due to variations in the measurement of insulin clearance or in the demographic groups. Additionally, reduced clearance may contribute to the early stage of hyperinsulinemia whereas hypersecretion may contribute only to the later stage.

Insulin clearance is associated with physical fitness and metabolic health. Aging is associated with reduced metabolic clearance of insulin and hyperinsulinemia, reduced glucose effectiveness, and an increase in metabolic diseases [92]. Likewise, metabolically healthy subjects with obesity have higher whole-body insulin clearance and hepatic insulin extraction compared with age- and BMI-matched subjects who are metabolically unhealthy [93]. Consistent with this, in nonobese Japanese men without diabetes, low insulin clearance was associated with higher total body fat and lower peak oxygen consumption rate [94].

Blacks had higher insulin levels than did whites and lower fasting c-peptide, consistent with impaired insulin clearance in blacks, which could not be explained by differences in BMI, family history, smoking, or other factors [95]. Lower metabolic clearance of insulin may explain the high prevalence of hyperinsulinemia in blacks. Hepatic first-pass insulin extraction has been estimated to be two-thirds lower in blacks compared with whites, whereas extrahepatic insulin clearance was similar [96]. This low first-pass hepatic extraction was also seen in African immigrants [97]. Consistent with this, in women without diabetes, blacks had a higher insulin response than did whites, as well as lower insulin clearance, but they had similar insulin secretion during OGTT, FSIVGTT, and a mixed meal tolerance test [98].

In IRAS-FS, blacks had lower metabolic clearance of insulin than did Hispanics, which was associated with hyperinsulinemia, greater SAT and VAT, lower high-density lipoprotein, and incident T2D [56, 99], and lower metabolic clearance of insulin was associated with lower insulin sensitivity, higher insulin secretion during FSIVGTT, and higher BMI across race and ethnicities [100].

Ethnic differences in insulin clearance are present in childhood. Black children had 63% higher first-phase insulin secretion and 14% lower clearance along with a 63% higher disposition index compared with whites with similar body composition and insulin sensitivity as assessed by hyperinsulinemic-euglycemic and hyperglycemic clamps [101]. Both greater insulin secretion and reduced clearance make independent contributions to the greater AIR in black children compared with white children [102]. Hispanic children also have a greater second-phase insulin secretion but have similar hepatic insulin extraction compared with

whites [103]. In adolescents with obesity, glucose effectiveness was greater in Hispanics than in blacks independent of total fat mass and visceral fat mass [104].

Insulin clearance in whites was lower in subjects with obesity and insulin resistance than in lean subjects, who were similar to subjects with obesity and normal insulin sensitivity [105]. Hyperinsulinemia in whites with obesity but without insulin resistance was mediated by increases in insulin secretion [106]. Additionally, there is evidence that insulin clearance may be associated with carbohydrate intake [107], body composition [108], liver fat [109], insulin sensitivity [110], acute hyperglycemia [111], and glucose intolerance [112]. Hence, both insulin clearance and secretion underlie the racial and ethnic differences in hyperinsulinemia.

C. Diet, Incretins, and Other Hormones Affect Insulin

Dietary differences may also contribute to hyperinsulinemia in black children. Blacks had a higher ratio of dietary fat intake to carbohydrate intake (determined by 24-hour recall), which was associated with higher FFAs, and reduced insulin sensitivity and insulin clearance, as well as upregulated β-cell function [113]. A high-fat diet was associated with reduced insulin sensitivity and insulin clearance in dogs [114, 115]. The short-term effects of lipid infusions on hyperinsulinemia and insulin clearance have shown mixed results [116, 117], but chronically higher FFAs have been associated with a decline in insulin secretion (adjusted for sensitivity) and reduced glucose effectiveness [118, 119].

During puberty, increases in GH, lipolysis, and insulin resistance contribute to hyperinsulinemia [120]. A longitudinal study showed that black girls had higher fasting insulin and AIR, earlier puberty, higher estradiol levels, higher FSH levels throughout puberty, and more rapid fat deposition after menarche compared with whites [121]. In a prospective cohort study of healthy Australian adolescent girls, insulin was negatively associated with ghrelin in boys and a positively associated with PYY [122]. Incretins may play an important role in the insulin response to glucose, as there were marked differences in glucose and insulin indices derived from OGTT and FSIVGTT in black and Hispanic adolescents with obesity [104]. GLP-1 may have paracrine and neural mechanisms to regulate insulin secretion, and hence its serum levels may provide only limited data on its metabolic effects, which makes it more difficult to study [123].

Fasting insulin was positively correlated with cortisol production rate in a study of 24 healthy men [124]. In adolescent girls with hyperinsulinemia and hyperandrogenism, free testosterone was negatively correlated with insulin resistance [125], although in normogonadal men, free testosterone was not associated with insulin sensitivity or β-cell function independent of its effects on adiposity [126]. A hyperinsulinemic-euglycemic clamp was shown to significantly increase ovarian androgen production in women [127]. Hyperinsulinemia contributes to hyperandrogenism in women with polycystic ovarian syndrome [128]. Hence, insulin secretion and sensitivity are associated with many factors, including HPA axis activation and sex hormones.

D. Reactive Oxygen Species, Redox, and Hyperinsulinemia

In vitro studies have suggested that hyperinsulinemia is associated with increases in reactive oxygen species. Exposing β-cells to excess lipids induces excess insulin secretion by increasing the mitochondrial redox state and production of reactive oxygen species, which in turn modulate the thiol redox state [129]. Supplementation with the antioxidant *N*-acetylcysteine was associated with an increase in HOMA-IR [130]. In healthy blacks without T2D, serum FFAs are positively associated with protein carbonyls, a marker of oxidative stress that were negatively associated with insulin sensitivity. This association was not seen in healthy whites, suggesting that blacks may be more sensitive to oxidative stress-induced insulin resistance than are whites [131]. Further studies of the redox state *in vivo* and its effects on insulin secretion and oxidative stress are needed.

4. Metabolic Consequences of Hyperinsulinemia

A. Acute Experimental Hyperinsulinemia

In healthy adults, hyperinsulinemia induced by a hyperinsulinemic-euglycemic clamp for 105 minutes increased inflammatory markers and β-amyloid in the cerebrospinal fluid and peripheral circulation [132]. Clamp studies in healthy subjects also demonstrated that chronic euglycemic hyperinsulinemia for 72 to 96 hours is associated with the development of insulin resistance and impaired nonoxidative glucose disposal [133]. The consequences of exposure to hyperinsulinemia may depend on the duration and magnitude of this exposure, as only 24-hour exposure to hyperglycemia and hyperinsulinemia was associated with increased insulin action and glucose effectiveness in healthy males [134].

B. Chronic Hyperinsulinemia

B-1. Hyperinsulinemia and incident diabetes

In youths with obesity, β-cell first-phase insulin secretion showed a stepwise decline from normal glucose tolerance to IGT to T2D [135]. Fasting insulin was an independent predictor of incident T2D in several cohorts [136, 137]. Hence, both postprandial and fasting hyperinsulinemia are associated with incident T2D. The AIR was not associated with subsequent weight gain in a longitudinal study of normoglycemic subjects during a mean time of 26 years [138]. However, the AIR in FSIVGTT does not reflect the incretin effect, and the insulin response to an oral glucose challenge may be a more physiologically relevant outcome. Hyperinsulinemia during an OGTT was associated with an atherogenic lipid profile in a sample of healthy Israelis [139]. Hyperinsulinemia was the most significant predictor of the progression to T2D in a study of 515 normoglycemic men in Israel during a 24-year follow-up period [140, 141]. In whites without diabetes, having a first-degree relative with T2D was associated with a loss of the normal relationship between BMI and insulin response to an OGTT and hyperinsulinemia even with a normal BMI [142]. Similarly, in the offspring of two parents with T2D, hyperinsulinemia was associated with the risk of developing T2D during an average follow-up time of 13 years independent of glucose removal rate [143].

Hyperinsulinemia may lead to incident T2D by affecting insulin resistance, fat storage, and/or direct effects on β-cells or other tissues. Normoglycemic women with a history of gestational diabetes are at increased risk of developing T2D and had significantly higher fasting insulin and fasting glucose, lower disposition index and insulin sensitivity, and reduced suppression of FFAs compared with women with no history of gestational diabetes [144]. The association between hyperinsulinemia and incident T2D and body composition has been seen in several other racial and ethnic groups, including Pacific Islanders [145] and Mexican Americans [146].

B-2. Hyperinsulinemia and NAFLD

In a prospective cohort study of 4954 Koreans without diabetes, baseline fasting hyperinsulinemia and increases in fasting hyperinsulinemia during a 5-year period were associated with incident NAFLD [147]. Fasting insulin was associated with hepatic steatosis in a sample of healthy Italians with normal transaminases [148]. Consistent with this, fasting insulin and insulin exposure during an IV glucose tolerance test were positively correlated with intrahepatocellular lipids, and subjects with NAFLD had higher intrahepatic insulin exposure than did healthy controls [149]. Compared with subjects without NAFLD, subjects with NAFLD had reduced hepatic insulin clearance and there was a negative correlation between hyperinsulinemia and both hepatic and whole-body insulin clearance [150].

Black women with obesity have a lower rate of TG turnover in adipose tissue and lower rates of adipose *de novo* lipogenesis (DNL) compared with white women with obesity [151].

DNL was originally thought to make only minor contributions to hepatic and adipose tissue lipid contents based on small studies in lean subjects [152]. However, technological improvement and studies in other populations have revealed that DNL is increased 2.4-fold from baseline fasting levels by an oral fructose challenge, and this increase in DNL was positively correlated with fasting insulin levels ($r = 0.75$) [153]. Blacks also tend to have lower intrahepatic TGs than do age- and BMI-matched whites, yet once NAFLD has developed the prevalence of nonalcoholic steatohepatitis may be similar [154].

B-3. Hyperinsulinemia, hypertension, and endothelial cell function

Insulin sensitivity and systolic blood pressure are the dominant determinants of endothelial function in blacks and whites [155]. Subjects with hypertension had higher meal-stimulated c-peptide secretion and lower insulin sensitivity compared with BMI-matched subjects with obesity without hypertension [156]. Similar findings were obtained in a study of Israelis that found that subjects with obesity and hypertension had a higher rise in serum insulin levels during an oral glucose test than did subjects with obesity and without hypertension [157]. Subjects with obesity had diminished endothelium-dependent vasodilation compared with lean controls during a hyperinsulinemic-euglycemic clamp [158]. Hence, hyperinsulinemia is associated with the vascular and lipid abnormalities associated with metabolic syndrome and may underlie its pathogenesis [159]. The exact mechanisms whereby loss of normal insulin pulsatility and hyperinsulinemia can lead to metabolic complications remain under investigation and are summarized in Fig. 2, and the molecular mechanisms for these pathways have been recently reviewed [160].

5. Therapeutic Implications

A. Differences in Insulin Metabolism May Underlie the Variability in the Response to Dietary Interventions

Racial differences in the response to dietary interventions may be mediated by differences in lipoprotein metabolism [161], which may explain the paradox that blacks have lower insulin sensitivity but often have lower TGs than do whites [162, 163].

Hyperinsulinemia may also modulate the effects of different dietary interventions. Compared with an isoenergetic high-fat low-carbohydrate diet, high simple carbohydrate diets are associated with higher rates of DNL and increases in TGs in lean subjects without hyperinsulinemia [164]. Subjects with hyperinsulinemia and obesity had significantly higher rates of DNL on a high-fat diet than did both subjects with obesity but without hyperinsulinemia and lean subjects without hyperinsulinemia [164]. Subjects with high insulin secretion may lose more weight on a low–glycemic index diet compared with a high–glycemic index diet [165]. Consumption of fructose has been associated with increases in serum insulin and reductions in insulin sensitivity in persons with overweight and obesity [166]. Isocaloric restriction of fructose for 10 days was associated with a significant decrease in liver fat, VAT, DNL, fasting insulin, fasting glucose, insulin secretion, and increased insulin clearance in blacks and Hispanic children with obesity [167]. The role of dietary fat and carbohydrates and insulin in the development of hyperinsulinemia and obesity is an active area of research and debate [168–170].

B. Bariatric Surgery Is Associated With Improvement in Hyperinsulinemia

Because obesity and hyperinsulinemia are often refractory to dietary and lifestyle changes, bariatric surgery is recommended for patients with severe obesity and comorbid conditions. Hyperinsulinemia may underlie the racial differences in bariatric surgical outcomes, such as blacks losing less weight than whites despite adjustment for clinical and behavioral factors

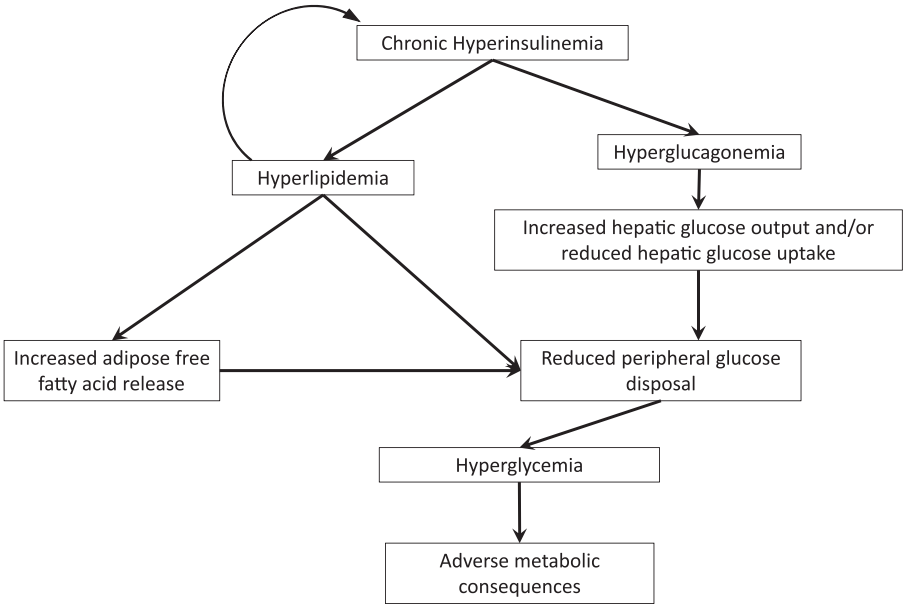

Figure 2. Diagram of potential mechanisms for hyperinsulinemia with altered insulin pulsatility to induce metabolic disease. Chronic hyperinsulinemia of any potential etiology is associated with chronic hyperglucagonemia, which may lead to increased hepatic glucose output. Nutrient excess and hyperlipidemia contribute to adipose tissue expansion and dysfunction with eventual ectopic lipid deposition, which is associated with reduced muscle glucose disposal.

[171] and blacks regaining more weight than whites in the years following surgery [172]. Bariatric surgery is associated with a rapid correction of hyperinsulinemia within 1 week of surgery, which may underpin its metabolic and clinical benefits. Unlike the rapid improvement in hyperinsulinemia after bariatric surgery, insulin sensitivity continues to improve between 6 and 24 months postoperatively whereas glucose effectiveness remained constant [173].

C. Exercise Training Is Associated With Improvement in Hyperinsulinemia

Male athletes have lower fasting glucose, lower insulin secretion, increased insulin sensitivity, and increased insulin clearance determined by the insulin/c-peptide ratio following a hyperinsulinemic-euglycemic clamp and arginine stimulation test compared with age- and BMI-matched sedentary males [110]. Consistent with this, exercise training has been shown to acutely lower insulin and gradually increase insulin sensitivity and glucose effectiveness [174, 175]. Compared with untrained subjects, endurance trained subjects had similar nonpulsatile basal insulin secretion, but significantly reduced insulin secreted per secretory burst [176].

D. Pharmacotherapies for Hyperinsulinemia

Hyperinsulinemia is not generally recognized as a primary therapeutic target although this has been debated [27]. Weight loss is associated with improvement in hyperinsulinemia with no change in glucose effectiveness, whereas weight gain is associated with worsening of hyperinsulinemia and reduced glucose effectiveness [177, 178]. Treating obesity with lifestyle modifications, dietary changes, pharmacotherapy, or metabolic surgery improves hyperinsulinemia acutely [179]. Liraglutide at 3.0 mg leads to greater weight loss and decreases in fasting insulin along with a reduction in incident diabetes in subjects with obesity but without diabetes [180].

Several other classes of medications can also affect insulin sensitivity and β-cell function. Fenofibrate, a PPARα agonist, increases fat oxidation and decreases insulin clearance and secretion in mice on a high-fat diet and warrants further trials in humans [181]. Bezafibrate, a pan-PPAR agonist, lowers both lipids and insulin [182]. However, the effectiveness of mediations directly targeting hyperinsulinemia has been mixed [183–186]. Further trials of new classes of medications that can attenuate hyperinsulinemia are warranted [187].

6. Conclusion

Strong evidence implicates hyperinsulinemia as an important precursor to the metabolic diseases associated with obesity. Environmental, genetic, and socioeconomic factors all contribute to the development and progression of hyperinsulinemia. Ethnic and racial differences in hyperinsulinemia are associated with differences in β-cell function and fat distribution. Dietary interventions have differing effects depending on underlying metabolic dysfunction. More research is needed to understand the effects of various genetic and environmental factors associated with hyperinsulinemia to determine which plays a causal role in metabolic disease. Such research in diverse populations will have implications for precision medicine.

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