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Hyperinsulinemia: Diagnostic and Treatment Considerations

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Abstract

Hyperinsulinemia may be the first indicator of developing metabolic disease and has been linked to insulin resistance, obesity, prediabetes, and type 2 diabetes. Diagnosis of hyperinsulinemia is complex, as signs and symptoms may not be present until other metabolic abnormalities have developed. Formal testing guidelines and a standardized approach to testing for hyperinsulinemia are needed. Practitioners can recommend and emphasize the importance of lifestyle modifications to prevent hyperinsulinemia and subsequent metabolic disease.

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Hyperinsulinemia and insulin resistance are two separate conditions, yet they are inextricably linked. Hyperinsulinemia is considered a compensatory response to insulin resistance. As cells are repeatedly exposed to large amounts of glucose, they become insulin resistant leading to an increase in insulin secretion and eventual hyperglycemia when beta cells fail to produce enough insulin. However, animal and human studies suggest that increased insulin secretion in response to overnutrition is actually the first event that then progresses to obesity and insulin resistance followed by type 2 diabetes (T2D) [1-4]. This model of diabetes development indicates that hyperinsulinemia, rather than glucose alterations, maybe the earliest sign of metabolic disease [2].

Data regarding the prevalence of hyperinsulinemia are limited. An analysis of 1999-2018 National Health and Nutrition Examination Survey (NHANES) data revealed rates of hyperinsulinemia increased by ~18% during that time period. When divided into time segments of 1999 to 2010 and 2010 to 2018, an increase of approximately 65% occurred in the first segment and a decrease of 29% was noted in the second segment, though the decrease did not reach the level of significance. Researchers theorized that the decrease may be related to improved medication regimens and lifestyle modifications [5].

The metabolic consequences of hyperinsulinemia justify the need for standardized diagnostic testing and clinical treatment guidelines. Hyperinsulinemia has been linked with the development of health conditions including T2D, obesity, dyslipidemia, hypertension, and cardiovascular disease [2-4,6-8]. Guidelines for the diagnosis and treatment of hyperinsulinemia in adults are not available. As a result, the detection of hyperinsulinemia before the cascade of events leading to insulin resistance, metabolic syndrome, and T2D is delayed. The purpose of this review is to present a synthesis of the literature on the role of hyperinsulinemia in the development of subsequent metabolic disease and provide evidence-based recommendations for interventions to decrease insulin levels in adults.

Methodology

For this narrative review, literature on the relationship of hyperinsulinemia, insulin resistance, and T2D was reviewed. Articles that included human or animal studies were included. Due to the small number of articles retrieved using a five-year limiter, the search was expanded to include articles published within the past 15 years. Databases searched included PubMed, MEDLINE, and CINAHL using the search terms “hyperinsulinemia”, “insulin resistance”, “dysglycemia”, “guidelines”, “laboratory testing”, “nutrition”, “diet”, “lifestyle interventions”, “diagnosis”, and “treatment”.

Hyperinsulinemia and Insulin Resistance

In an article that reviewed the role of hyperinsulinemia in the development of other conditions, Janssen reported that a large percentage of people with normal glucose tolerance have hyperinsulinemia before impaired glucose tolerance or obesity develops [4]. In a systematic review of 423 prospective, retrospective, and cross-sectional studies, hyperinsulinemia was present in a number of disorders that are linked to metabolic syndrome (e.g., obesity, diabetes, hypertension, dyslipidemia). The researchers proposed a syndrome of hyperinsulinemia as a causative condition rather than an event that occurs secondary to these conditions [7]. In a secondary data analysis of 7,755 participants who had plasma glucose and plasma insulin levels drawn following a glucose tolerance test, Crofts C, et al. (2016) [2], found that the majority of participants with normal glucose metabolism had hyperinsulinemia. Approximately 75% of those with normal glucose tolerance and 90% of those with impaired

glucose tolerance were affected by hyperinsulinemia. The majority of participants who were hyperinsulinemic were not obese, the mean body mass index was 26.9, which calls the theory that obesity leads to insulin resistance into question [2].

Erion KA, et al. (2017) [8], reported that elevated lipids, elevated insulin levels, and insulin resistance precede the development of metabolic disease [8]. Further, they stated rodent models indicate that hyperinsulinemia precedes insulin resistance and may actually contribute to it. Erion KA, et al. (2018) [3], noted that rodents treated with exogenous insulin or that overexpressed the human insulin gene developed insulin resistance secondary to hyperinsulinemia [3]. Corkey BE (2012) [1], reported examples of hyperinsulinemia preceding insulin resistance, including studies that artificially increased circulating insulin in humans and rodents which led to insulin resistance and weight gain [1].

In a longitudinal study with a 24-year follow-up of 515 normoglycemic Israeli participants with ethnic origins from North Africa, Yemen, the Middle East, and Europe-America, half of the cohort progressed to dysglycemia (12-h fasting plasma glucose > 100 mg/dL and/or 2-h post-load glucose >140 mg/dL), while the other half remained normoglycemic [9]. Predictors of progression to dysglycemia included male gender, hyperinsulinemia, high body mass index, elevated blood pressure, and elevated blood glucose. Basal hyperinsulinemia, defined as elevated fasting insulin levels, was found to be the strongest predictor with the risk of developing dysglycemia being almost twice as high for participants in the upper quintile of fasting insulin than for the other four quintiles combined [6]. Pories and Dohm presented data that showed baseline insulin levels rise as patients move through the stages of a healthy lean state to T2D [10]. Patients with T2D and fasting blood glucose levels greater than 140 had baseline insulin levels nine times higher than those of lean patients with normal glucose tolerance. This data indicates the problem lies in too much insulin production during the fasting state and aligns with the finding that hyperinsulinemia was predictive of T2D in the Dankner R, et al. (2009) [9], 24-year follow up study.

Hyperinsulinemia and Weight

Elevated insulin levels are associated with weight gain, overweight, and obesity due to the increased uptake and storage of glucose. A series of studies with mice found that excess insulin contributed to diet-induced obesity [11]. Other research with mice found that insulin levels were elevated several weeks before onset of obesity and a high fat diet induced pancreatic insulin hypersecretion followed by obesity [12]. Two longitudinal studies with healthy, normoglycemic children supported hyperinsulinemia as a predictor of increased body weight [13,14]. Kolb H, et al. (2020) [15], noted that increases in insulin levels inhibit lipolysis and increase lipogenesis, without inhibiting gluconeogenesis leading to increased body mass index. Kolb H, et al. (2018) [16], reported that in studies with adults where a pharmaceutical agent, octreotide or diazoxide, was taken to lower insulin levels, significant weight loss occurred in association with lowered insulin levels. A study involving insulin-sensitive lean and obese participants found basal and postprandial insulin secretion rates to be more than 50% higher in the obese participants. Additionally, a weight loss of at least 15% in participants with obesity decreased insulin secretion by 35% [17].

Hyperinsulinemia and Other Health Conditions

Early detection of hyperinsulinemia is important because of its proclivity over time to contribute to other health conditions including T2D, dyslipidemia, hypertension, and coronary artery disease (CAD) [6]. A systematic review conducted to determine the presence of hyperinsulinemia in various health conditions found that hyperinsulinemia was present in other conditions including renal failure, nonalcoholic fatty liver disease, polycystic ovarian syndrome, sleep apnea, certain cancers, atherosclerosis, and cardiovascular disease [4]. The researchers determined that health conditions linked to metabolic syndrome are also linked to hyperinsulinemia which may indicate a common pathology. Previous research revealed associations between hyperinsulinemia and genetic, environmental, and dietary factors [4]. Further, findings suggested that hyperinsulinemia is the primary factor in the development of T2D and insulin resistance is a secondary response due to excess exposure to insulin [7]. Evidence supports that hyperinsulinemia precedes hyperglycemia so that by the time increases in blood glucose are observed, damage has already occurred to beta cells [18]. Early detection of disease is correlated with better outcomes; therefore, diagnosis and treatment of hyperinsulinemia prior to hyperglycemia could lead to a reduction in hyperglycemia and thus T2D.

Diagnosis of Hyperinsulinemia

Diagnosing hyperinsulinemia presents a challenge for healthcare providers as signs and symptoms are typically not present in patients until insulin resistance, metabolic dysfunction, or disease has already occurred [19-21]. Hyperinsulinemia is often described as the "silent disease", as many patients, excluding those with insulinomas, nesidioblastosis, or congenital hyperinsulinism, will not present with specific symptoms [4]. If patients do present with symptoms, those may include mood swings, frequent hunger, cravings for sugar, anxiety, weight gain, amenorrhea, lack of focus, and/or fatigue. These nonspecific signs pose a challenge for practitioners, as these symptoms may be related to a number of other conditions, not specifically hyperinsulinemia [22].

While diagnostic criteria and guidelines exist for insulin resistance, T2D, and metabolic syndrome, the same cannot be said for hyperinsulinemia, except in the case of congenital hyperinsulinism. The National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATP III), the World Health Organization (WHO), the American Association of Clinical Endocrinologists (AACE), and the International Diabetes Federation (IDF) have developed diagnostic criteria to identify patients with insulin resistance/metabolic syndrome (Table 1). While the most widely used criteria in the United States (U.S.) is the NCEP/ATP III, definition(s) of, sensitivity/specificity of, and clinical value in the use of various diagnostic criteria has been debated by various healthcare organizations, associations, and researchers [20,23]. There remain several definitions and criteria for metabolic and/or insulin resistance syndrome making analyzing data from clinical research and choosing which criteria to standardize across clinical practice challenging [24]. However, most healthcare organizations and associations agree that many traits of metabolic syndrome co-exist along with insulin resistance, or that hyperinsulinemia is a key pathophysiologic component in the development of insulin resistance [19,20,24, and 25]. This being the case, practitioners should be aware of patient risk factors for hyperinsulinemia, insulin resistance and/or prediabetes, including overweight, obesity, central adiposity, sedentary lifestyle, age 35 or older, family history of diabetes, ethnicity, physical inactivity, high blood pressure, abnormal cholesterol levels including low high-density lipoprotein (HDL) and/or high triglyceride level, history of gestational diabetes, heart disease, or stroke, and PCOS [26,27].

The "gold standard" for assessing insulin sensitivity is the hyperinsulinemic-euglycemic clamp (HIEC) technique; however, this method is not appropriate for epidemiological or sizeable studies, nor the clinical setting, as it is expensive, laborious, invasive, requires trained personnel, and may not accurately reflect insulin action [28-31]. The homeostatic model assessment for insulin resistance (HOMA-IR) is the most frequently used method to estimate insulin resistance from fasting glucose and fasting insulin concentrations (fasting plasma insulin (FPI) x fasting plasma glucose (FPG) ÷ 22.5) between or within groups in large epidemiological studies and population-based clinical trials [30,32-34]. The quantitative insulin sensitivity check index (QUICKI) provides an estimation of insulin sensitivity and like the HOMA-IR, a log transform of insulin glucose product is used (QUICKI = 1/ [log (fasting glucose) + (log (fasting insulin)] [20,30]. There are advantages to the HOMA-IR and QUICKI models, as they are less expensive and invasive than the HIEC, only require one blood draw from a fasted patient, and some studies indicate their significant and strong correlation with HIEC indices [30,33-35]. Research demonstrates that elevated HOMA-IR and QUICKI levels are associated with adverse health outcomes in the general population and in patients with various comorbidities; therefore, some research suggests both tests may be suitable to use in clinical practice [30,33, and 36-42]. However, the HOMA-IR may be limited due to the lack of standardized reference intervals, potential variations in healthy HOMA-IR levels across ethnicities, ineffective use in patients with poor glycemic control and those treated with insulin, and the lack of standardized insulin assays [32-34]. The HOMA-IR or QUICKI are not currently recommended as standard assessments of insulin resistance and/or hyperinsulinemia in the clinical setting [19,32].

Several other indirect measures, as well as indicators or surrogate markers, have been developed over the years to assess for hyperinsulinemia and/or insulin resistance in a clinical setting. The insulin-to-glucose ratio may be utilized by some clinicians, as high insulin levels with normal glucose levels are indicative of insulin resistance [33]. This tool is an imperfect indicator of insulin sensitivity in the general population as it should be used in the early stages of hyperinsulinemia and/or insulin resistance before pancreatic beta cells begin to fail, which is clinically difficulty to determine [32,33]. The triglyceride-glucose (TyG) index is a simple and reliable marker of insulin resistance, however more research is indicated to evaluate the specificity and sensitivity for use in the clinical setting [43,44]. Research suggests other laboratory tests to assess for insulin resistance can be utilized with normotensive overweight patients include fasting insulin levels, triglyceride concentrations, ratios of triglyceride to high-density lipoprotein (HDL) cholesterol concentrations, and ratios of total cholesterol to HDL concentrations [21,25,31,32, and 45]. These cholesterol tests are not recommended to diagnose insulin resistance clinically, as the sensitivity and specificity thresholds are below 90% [32].

As there are no standardized diagnostic criteria and/or current guidelines on hyperinsulinemia screening or testing, practitioners should utilize guidelines and recommendations in screening patients for insulin resistance (Table 1), metabolic syndrome (Table 1), and/or prediabetes/T2D (Table 2). Practitioners may order basic lab tests, such as blood glucose, hemoglobin A1C (HgA1C), and lipid panels as well as other diagnostic measures such as blood pressure, waist circumference, weight, and BMI based on clinical presentation and assessment [26]. The measurement of fasting insulin levels and/or an insulin-to-glucose ratio in the clinical setting is not widely used, even though fasting insulin levels are an independent determinant for the future development of metabolic syndrome as well as a parameter that can relate to the patient's degree of insulin resistance and/or hyperinsulinemia [21,25].

Table 1: Insulin resistance diagnostic criteria.

Organization	Criteria
NCEP/ATP III criteria for metabolic syndrome (*diagnosis is made when 3 or more are present*):	• A waist circumference of more than 120 cm (47 inches) in men or more than 88 cm (35 inches) in women • Fasting triglyceride level of 150 mg/dL or higher • The blood pressure level of 130/85 mmHg or higher • High-density lipoprotein cholesterol (HDL-C) level of less than 40 mg/dL in men or less than 50 mg/dL in women • Fasting glucose level of 100mg/dL
WHO criteria for metabolic syndrome:	• Type 2 diabetes • Impaired fasting glucose (IFG) of 101-125 mg/dL • Impaired glucose tolerance (IGT): glucose level of 140-199 mg/dL 2 hrs. after administration of 75 g of glucose • Glucose uptake level less than the lowest quartile for ethnic populations under hyperinsulinemic, euglycemic conditions if the fasting glucose level is normal *Diagnosis must also include 2 of the following: • Use of antihypertensive medication; blood pressure of 140 mmHg systolic or higher, 90 mmHg diastolic or higher, or both • Triglyceride level of 150 mg/dL or higher • HDL-C level of less than 35 mg/dL in men or less than 39/dL in women • Body mass index (BMI) of more than 30 kg/m^2, a waist-to-hip ratio of more than 0.9 in men or more than 0.85 in women, or both • Urinary albumin excretion level of 20 mcg/min or higher or albumin-creatinine ratio of 30 mg/g or higher
AACE clinical criteria for insulin resistance syndrome	• BMI of 25 kg/m^2 or higher • Triglyceride level of 150 mg/dL or higher • HDL-C level of less than 40 mg/dL in men or less than 50 mg/dL in women • Blood pressure of 130/85 mmHg or higher • IGT: Glucose level of more than 140 mg/dL 2 hours after administration of 75 g of glucose • Fasting glucose level of 110-126 mg/dL
IDF global diagnostic criteria for metabolic syndrome	• Central obesity (waist circumference ≥ 94 cm in men or ≥ 80 cm in women in Europid persons and in ethnic-specific levels in Chinese, Japanese, and South Asian persons) *Along with 2 of the following: • Triglyceride level of 1.7 mmol/L (150 mg/dL) or higher • Low HDL-C level (defined as <1.04 mmol/L [40 mg/dL] in men or < 1.29 mmol/L [50 mg/dL] in women) • Blood pressure of 130.85 mmHg or higher • Fasting hyperglycemia (defined as glucose levels ≥ 5.6 mmol/L [100mg/dL] or previous diagnosis of diabetes or IGT

Table 2: Screening for prediabetes and type 2 diabetes.

Organization	Criteria
US Preventative Services Task Force	· Adults aged 35 to 70 years who have overweight or obese (BMI ≥ 25 and ≥ 35, respectively) · Consider screening earlier if the patient is American Indian/Alaska Native, Black, Hawaiian/Pacific Islander, Hispanic/Latino, and at a lower BMI (≥ 23) if the patient is Asian American · Recommended laboratory tests and results: o Indicative of diabetes: Fasting plasma glucose level of 126 mg/dL or greater, HgA1C level of 6.5% or greater, or a 2-hour post-load glucose level of 200mg/dL o Indicative of pre-diabetes: Fasting plasma glucose level or 100 – 125 mg/dL, HgA1C level of 5.7% to 6.4%, or a 2-hour post-load glucose level of 140 to 199 mg/dL
American Diabetes Association	· All adults over 45 years or older, regardless of risk factors · Screening for all adults who have overweight or obesity (BMI ≥ 25 or ≥ 23 in Asian American persons) with 1 or more risk factors, regardless of age · Screening should occur every 3 years at a minimum · Recommended laboratory tests: o Fasting plasma glucose level o Or 2-hour plasma glucose level during a 75-g oral glucose tolerance test o Or HgA1C level

Interventions for Hyperinsulinemia

Because of the lack of a standardized diagnostic test for hyperinsulinemia, interventions to treat hyperinsulinemia are limited to lifestyle modifications. Medications such as octreotide and diazoxide have been used to treat hyperinsulinemia secondary to congenital conditions that lead to hypoglycemia such as insulinomas. In the case of hyperinsulinemia as a triggering event for insulin resistance where hypoglycemia is not present, there are no recommendations for prescribing these medications. If patients do not see an immediate health threat that a positive diagnostic test can provide, they may be disinclined to adhere to specific preventive interventions. However, healthcare providers should provide education about the risks of hyperinsulinemia and primary prevention strategies to promote health. The Adult Treatment Panel III (ATP III), the American Heart Association (AHA), the National Institutes of Health (NIH), and the Endocrine Society agree that lifestyle modifications, including aggressive weight reduction and increased physical activity, are first-line recommended therapeutic goals in patients with or at risk for hyperinsulinemia, insulin resistance, or metabolic syndrome [24].

Several dietary patterns have shown effective in the prevention and treatment of insulin resistance, including the Mediterranean Diet, the Dietary Approaches to Stop Hypertension (DASH) diet, a high-fiber plant-predominant diet, and a diet consisting of foods with low glycemic index [19,21,24, and 46-48]. There is conflicting evidence in the research regarding certain eating patterns, as certain literature suggests a ketosis-inducing with or without calorie restriction may be beneficial in the treatment of insulin resistance, while several studies discuss the role increased animal protein and saturated fats play in the development of hyperinsulinemia and insulin resistance [46,49-51]. Evidence suggests a link between low sugar intake and reduced fasting insulin levels, while low-calorie diets and intermittent fasting lead to lower insulin levels throughout the day, thus improving circulating insulin levels [16,52]. There is clear evidence from the Diabetes Prevention Program and its Outcomes Study (DDP & DPPOS) that a dietary eating pattern including sodium reduction, caloric restriction, fat reduction, and noting the glycemic index of foods was effective in the prevention of diabetes in high-risk adults, further solidifying the need for nutrition research specific to the prevention and treatment of hyperinsulinemia and/or insulin resistance [19].

Physical activity, including aerobic exercise and resistance training, is an effective method to improve insulin sensitivity, as well as assist with weight reduction and maintenance [2,21, and 24]. Aerobic exercise is beneficial in improving insulin resistance and glycemic control in patients of any age, whether healthy/asymptomatic or in patients with comorbidities [53]. There is a large amount of research on the benefit of aerobic exercises, such as walking, jogging, biking, and swimming, however, specific activity prescription should be based on the individual patient and current activity level. Current evidence-based recommendations for health promotion and disease prevention include 150 minutes per week of moderate-intensity aerobic activity [54]. Resistance training, or strength training, overall health benefits are globally recognized, and research shows its benefit in reducing abdominal and total body fat, increasing strength and metabolic rate, decreasing the risk of falls, lowering the risk of injury, improving cardiovascular health, mobility, and flexibility, optimizing blood glucose levels, and lowering the risk of all-cause mortality [55,56]. Resistance training may also improve hyperinsulinemia by enhancing glucose utilization, and cellular metabolism, and maintaining or increasing muscle mass [2]. The American College of Sports Medicine recommends resistance training be performed a minimum of 2 non-consecutive days per week and should be based on the individual patient's current activity level [57]. Davidson LE, et al. (2009) [58], found that the combination of aerobic and resistance exercises is effective in reducing insulin resistance in previously sedentary obese adults.

Conclusion

Research presented in this review indicates that hyperinsulinemia may be an independent risk factor for obesity and may be one of the earliest indicators of T2D since increases in insulin levels occurred before changes in blood glucose levels. As a result, decreasing insulin levels can lead to weight loss and the prevention of T2D. Currently, there are no formal guidelines for the diagnosis of hyperinsulinemia. There is a need for standardized recommendations/guidelines for the measurement of insulin levels in people with normal blood glucose to predict and prevent future metabolic diseases. If signs and symptoms or risk factors are present, practitioners can evaluate insulin, glucose, HgA1C, and other levels; however, as indicated by existing literature, patients may be hyperinsulinemic without symptoms. The challenge is detecting hyperinsulinemia before the cascading events of insulin resistance and T2D occur. The ability to detect possible hyperinsulinemia is hampered by the lack of insurance coverage for those who may be at risk but are not symptomatic at present. Until standardized diagnostic measures and practice guidelines for hyperinsulinemia are developed, practitioners must take a multidimensional approach to prevent hyperinsulinemia by first assessing the lifestyle factors of patients that put them at risk for hyperinsulinemia and subsequent insulin

resistance and metabolic disease. Practitioners should educate patients on effective lifestyle modifications, including diet and physical activity. Dietary patterns, such as the Mediterranean Diet and the Dash diet, are shown to prevent and treat insulin resistance. Patients should be encouraged to achieve 150 minutes per week of moderate-intensity aerobic activity as well as at least two days of resistance training to improve hyperinsulinemia.

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