Metabolic Syndrome Pathogenesis: Evidence from Monogenic Disorders

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Received: 28-Sep-2022, Manuscript No. jdm-22-20133; **Editor assigned:** 01-Oct-2022, PreQC No: jdm-22-20133(PQ); **Reviewed:** 08-Oct-2022, QC No. jdm-22-20133; **Revised:** 22-Oct-2022, Manuscript No. jdm-22-20133(R); **Published:** 31-Oct-2022, DOI: 10.35248/2155-6156.1000958

Abstract

The discovery of uncommon human metabolic disorders caused by a single gene defect has not only improved the diagnosis and clinical care of these patients, but it has also provided important biological insights into the pathophysiology of the metabolic syndrome, which is becoming more and more common. Obesity, which is fuelled by calorie excess and decreased physical activity, is a risk factor for type 2 diabetes and insulin resistance. However, it can be challenging to separate important events in the metabolic syndrome's aetiology from compensatory effects and epiphenomena. The three human monogenic illnesses that cause severe, non-syndromic obesity, pancreatic beta cell variants of early-onset diabetes, and severe insulin resistance are described in this article. The primary defect is known in these patients who have single-gene defects causing their exaggerated metabolic disorder. It is emphasised what they can teach us about the common metabolic syndrome's molecular pathogenesis today.

Keywords: Diabetes; Diagnosis: Monogenic; Obesity; Metabolic

Introduction

The aetiology of the twin epidemics of type 2 diabetes and obesity is thought to include insulin resistance. Globally, these diseases have a large burden of premature morbidity and mortality; yet, there is some interdependence between them. Despite significant research, the molecular mechanisms underlying the metabolic syndrome's link between obesity, insulin resistance, and type 2 diabetes remain poorly understood. Over the past 20 years, there has been an increase in the number of single-gene defects that cause rare forms of diabetes, obesity, or severe insulin resistance [1]. This has given researchers the chance to better understand the cause-and-effect relationships between various key mediators in these various groups of disorders. We list the main monogenic diseases that cause severe insulin resistance, pancreatic beta-cell diabetes, or nonsyndromic obesity and explore how the knowledge they offer can be used to better understand other common metabolic diseases [2].

Monogenic Nonsyndromic Obesity

Proof That Single-Gene Defects Controlling Important Central Aspects of Appetite Can Cause Obesity in Humans Obesity, at its most basic level, is the outcome of excessive energy intake exceeding energy expenditure over an extended period of time. The rapid rise in the prevalence of overweight and obesity over the past 30 to 40 years implies that environmental, dietary, and lifestyle variables have changed more rapidly than genetics as the primary contributors to the obesity pandemic. However, it is evident that there are significant hereditary components to both the risk of becoming fat and the comorbidities that go along with it. In the past two decades, there has been a greater knowledge of the mechanisms governing energy balance and, in particular, appetite management [3].

Leptin and Leptin Receptor Mutations

One of the first hormones involved in energy balance to be discovered and confirmed to be lacking in the extremely obese ObOb mice model of obesity is leptin. Adipocytes secrete leptin in proportion to adipose tissue mass, and women have higher blood levels of leptin than males do. One of leptin's key biological activities is in the regulation of appetite by signalling adipose storage via binding to leptin receptors in the arcuate nucleus of the hypothalamus [4]. Leptin also has impacts on reproduction, bone mineral density, and the immune system. Additionally, leptin plays a crucial role in reproduction. Leptin alerts the hypothalamus when there is enough adipose storage to start puberty. Leptin therefore has a favourable impact on puberty. Additionally, gonadotrophin levels and pulsatility are impacted, which inhibits ovulation, if adipose storage decline and leptin levels drop [5].

The observations of O'Rahilly et al., who identified children with severe early development of obesity who had undetectable levels of leptin, provide evidence for the crucial role of leptin in energy management in humans. They were discovered to be homozygous for a leptin gene frameshift mutation that produced a shortened protein that was not released. They had excess fat mass, hyperphagia, and were morbidly obese, but neither their resting metabolic rate nor their total energy expenditure, which had been adjusted for body composition, changed. These kids had a recessive homozygous mutation in the leptin gene, making them human versions of obese (ob/ob) mice [6]. This study established the importance of leptin in controlling human appetite. This was supported by the finding that recombinant human leptin replacement in these kids quickly reversed the hyperphagia, encouraged weight loss, and normalised body composition. The discovery of a leptin receptor mutation and the description of persons with homozygous lack of leptin receptor function provide additional evidence for the significance of leptin. Although these people have very high levels of circulating leptin, their phenotype is very similar to that of leptin-deficient people. They do not, however, respond to treatment with additional leptin, as would be expected [7].

Monogenic Pancreatic Beta Cell Diabetes

Evidence of Important Pancreatic Beta Cell Function Elements and Response of Some Genetic Etiologies to Oral Glucose-Lowering Drugs Taking action proximally to the monogenic defect, in the absence of obesity or insulin resistance, beta-cell monogenic diabetes is characterised by genetic abnormalities that cause early onset diabetes. The majority of the earlier mutations were discovered using the candidate gene approach, which involves choosing genes that are known to be important for beta cell function and then showing that a mutation causes critical beta cell dysfunction in both laboratory settings and in people who already have mutations. The physiology of normal beta cells has lately been further illuminated by the discovery of unique and unexpected mutations that cause beta cell malfunction [8].

The pancreatic islets of Langerhans, which make up 1-2% of the overall pancreatic mass, are primarily made up of beta cells. The three essential roles performed by a typical human beta cell are necessary for it to contribute to the maintenance of normal blood sugar levels. The beta cell must first be able to "detect" ambient glucose levels so that any insulin production can be tailored to the needs. Next, the beta cell must be able to produce and store insulin. Finally, the cell must be able to secrete insulin quickly when needed. Any of these roles that are dysfunctional will affect the glucose homeostasis. Neonatal diabetes mellitus (NDM) and other early-life manifestations of diabetes are typically thought to be caused by mutations that are more intrinsic to this process than those that manifest later in life; however, the genotype-phenotype relationship for the majority of pancreatic beta cell mutations is still unknown [9].

Materials and Methods

Mutations in the INSR gene result in a clinical spectrum of disease severity ranging from mild to severe. Less severe disease is usually caused by an autosomal dominant gene mutation in the INSR gene, in which patients present in the peri-pubertal stage or beyond with acanthosis nigricans, dysglycemia (either fasting hypoglycemia and postprandial hyperglycaemia or frank diabetes) in the presence of severe hyperinsulinemia, oligomenorrhea, and hyperandrogenism in women. In men, the presentation is less obvious with only acanthosis nigricans and sometimes fasting hypoglycaemia. Men often remain undiagnosed even after the development of diabetes requiring high doses of insulin [10].

Extreme insulin resistance is present in patients with Donohue syndrome and Rabson-Mendenhall syndrome, two of the most severe disorders caused by rare autosomal recessive mutations in the insulin receptor gene. These disorders are characterised by a nearly complete loss of residual insulin receptor function. Clinical signs include poor muscle and adipose tissue development, fasting hypoglycemia, postprandial hyperglycemia, severe hyperinsulinemia, and intrauterine and postnatal growth limitation. Donohue syndrome typically results in death from concurrent infection, but Rabson-Mendenhall syndrome is distinct because it also includes dysplastic dentition, coarse facial characteristics, severe diabetic ketoacidosis, pineal hyperplasia, and survival past infancy [11].

Because they have higher levels of adiponectin, sex-hormone-binding globulin (SHBG), and insulin-like growth factor-binding protein 1 than people with more common insulin resistance linked to the metabolic syndrome, patients with INSR mutations are distinguished from those with that condition biochemically (IGFBP1). In individuals with obesity-related insulin resistance and various lipodystrophies, adiponectin, SHBG-, and IGFBP1 are all frequently decreased; therefore, these markers are useful for diagnosing individuals with insulin receptor dysfunction from those with other severe insulin resistance-inducing conditions [12].

People with the insulin receptor mutation have very high levels of circulating insulin that can bind to the insulin-like growth factor-1 (IGF1) receptor and stimulate the development of polycystic ovaries and acanthosis nigricans. This model of partial insulin resistance highlights different tissues in these people. Those with insulin receptor mutations do not have fatty livers or the suppression of insulin-like growth factor binding protein 1 (IGFBP1), sex hormone binding globulin (SHBG) [13], or adiponectin, which most likely requires active signalling through the no glucose metabolism arms of the insulin receptor substrate (IRS) downstream path, unlike those with AKT2 (v-akt murine thymoma viral oncogene homolog (2) mutations and those with The individual set point up to which adipose tissue can be expanded without metabolic morbidity is represented by the tissue expandability theory model in (b), which is likely to depend on genetic factors. The two curves depict the relationship between gaining weight and losing insulin sensitivity; however, the curve on the left depicts the extremely constrained adipose expandability in people with lipodystrophy, whereas the curve on the right depicts people with the more common obesity-associated reduction in insulin sensitivity [14].

Discussion

Although studies of monogenic cases of insulin resistance were looked at for the effect of hyperinsulinemia on actions like suppressing hepatic lipogenesis, it was not until then that the possibility of partial insulin resistance was made clear. Hyperinsulinemia in the context of normal blood glucose is frequently thought to be the hallmark of insulin resistance. In contrast to patients with INSR mutations who did not, it has been demonstrated that patients with primary lipodystrophy, AKT2 mutations, or severe insulin resistance of unknown cause exhibit increased forms of metabolic dyslipidemia and fatty liver. In contrast to those with AKT2 mutations, those with INSR mutations had normal hepatic de novo lipogenesis along with normal lipid profiles [15].

Numerous genes have autosomal recessive mutations (either homozygous or compound heterozygous) that have been linked to the pathophysiology of CGL. The majority of instances are caused by mutations in two genes, 1-acylglycerol-3-phosphate-O-acyltransferase 2 (AGPAT2) and Berardinelli-Seip congenital lipodystrophy 2 (BSCL2). These mutations were found in affected families using linkage analysis and positional cloning. One of the essential enzymes involved in the production of triglycerides and phospholipids from glycerol-3-phosphate is AGPAT2, which is abundantly expressed in adipose tissue. Seipin, a protein produced by BSCL2, is considered to have a role in lipid droplet production and adipocyte differentiation. It is abundantly expressed in the brain and adipose tissue. Similar metabolic problems are present in patients with both AGPAT2 and BSCL2 mutations, however there are some clear clinical distinctions [16].

Family partial lipodystrophy (FPL) of the Dunnigan variant was first linked to the lamin A/C (LMNA) gene, which is still the most frequent cause of FPL. Mutations in LMNA which codes for the nuclear lamina protein lamin A/C, have also been related to a variety of other diseases, including limb-girdle muscular dystrophy, progeria syndromes, restricted dermopathy, and mandibulo-acral dysplasia. Peroxisome proliferator-activated receptor gamma (PPARG), a nuclear hormone receptor that is primarily expressed in adipose tissue, was the second gene to be discovered in FPL. It is crucial for adipocyte differentiation and a target for the class of diabetic drugs known as thiazolidinedione. Since then, other genes have been discovered, including perilipin 1, AKT2, and cell-death inducing DFFA-like effector c (CIDEC) (PLIN1). The dynamics of lipid droplets and the control of triglyceride mobilisation are both influenced by CIDEC and PLIN1 [17].

In all of these FPLs, women are affected significantly more severely than men and the failure of fat development frequently does not become apparent until puberty. This may be connected to the higher levels of obesity in girls than in males, especially when puberty begins. Although it is unclear whether there is phenotypic variation across the several genetic variants of FPL, all kinds exhibit a partial loss of subcutaneous fat in the extremities. While there is maintained abdominal fat in the other forms, the LMNA variety similarly affects the trunk while sparing the face and neck [18]. The lipodystrophies show that a certain quantity of adipose tissue is needed to act as a sump for free fatty acids and glucose to buffer episodic excess caloric intake. In other metabolically unsuited tissues including the liver, muscle, and pancreatic beta cells, where adverse effects include fatty liver, dyslipidemia, loss of insulin sensitivity, and decreased insulin output, higher absorption results from the loss of this capacity. The loss of adipocyte-tissue-derived leptin, which alerts the brain when adipose tissue is adequate, may be an aggravating factor. Leptin loss in CGL (and to a lesser extent FPL) indicates that the body's energy reserves are low, which causes compensatory hyperphagia. Systemic metabolic stress is exacerbated by the subsequent increase in calories consumed. The remarkable effectiveness of leptin replacement in patients with the majority of lipodystrophies serves as evidence of this [19].

The adipose expandability concept is supported by the uncommon lipodystrophy disorders. According to this, people have a fixed ability for adipose tissue to expand in response to excessive energy consumption (very low in those with lipodystrophy but very high in those with morbid obesity without associated features of metabolic syndrome). Chronic calorie intake above this threshold causes fat to accumulate in other organs like the liver, skeletal muscle, and pancreatic beta cells where it can lead to fatty liver, dyslipidemia, insulin resistance, and diabetes (more slowly in those with lipodystrophy and more quickly in most people with common metabolic syndrome) [20].

Conclusions

It is very effective in demonstrating how defects in specific encoded proteins located primarily in the brain, pancreatic beta cell, muscle, and or fat give rise to these distinct components of the metabolic syndrome that loss of function of specific genes in humans causes either severe obesity, early diabetes, or severe insulin resistance (with or without lipodystrophy). They contest the theory, which has been backed by several cross-sectional and longitudinal epidemiological studies that obesity brought on by the environment causes insulin resistance, which causes type 2 diabetes. The monogenic illnesses offer unique insights into: (1) the molecular underpinnings of obesity, which alter appetite and predispose to type 2 diabetes and insulin resistance, in the absence of either obesity or insulin resistance, specific defects in pancreatic beta cell function predispose to diabetes. In addition, specific defects in insulin signalling or fat storage capacity can cause severe insulin resistance in the absence of obesity, which then causes diabetes by exhausting the pancreas. It has been determined that all single-gene abnormalities linked to

human obesity affect hunger. The same processes appear to be affected by frequent genetic variations that predispose to obesity.

From early childhood through early adulthood, diabetes is a common monogenic pancreatic beta cell disorder caused by critical abnormalities in the insulin secretory pathway. Based on the position of the genetic defect upstream from the target of the sulfonylurea medicine, certain monogenic subtypes of diabetes have resulted in dramatic success when shifting from insulin therapy to oral sulfonylurea therapy. Some of these findings can be applied to the genesis of type 2 diabetes since the confounding effects of obesity are less significant in these conditions. Numerous beta cell targets that overlap with recognised causes of monogenic diabetes share common genetic variations that predispose to type 2 diabetes. Type 2 diabetes is currently thought to be predominantly caused by inadequate glucose-stimulated insulin production, but the exact location of the beta cell malfunction remains unknown. The monogenic diabetes phenotypes taken together with type 2 diabetes' transient response to SU therapy suggest that multiple processes downstream of mitochondrial metabolism and the KATP channel within the pancreatic beta cell, which control the amplification response to glucose or insulin exocytosis itself, are involved in type 2 diabetes. As is the case in cases of severe insulin resistance, the associated obesity-related insulin resistance in type 2 diabetes is likely to increase the functional demand on the beta cell and hasten beta cell failure.

Contrary to the popular observation that insulin resistance is associated with obesity, people with monogenic abnormalities leading to severe insulin resistance often do not have obesity or have a generalised or localised lack of adipose tissue. A failure in triglyceride storage in adipose tissue occurs in such lipodystrophic patients from many hereditary causes of fat metabolism, which causes lipid build-up elsewhere in the body. As a result, there is substantial insulin resistance, along with the usual symptoms of fatty liver and atherogenic dyslipidemia. Directly speaking, individuals with defects in their insulin receptors have extremely high levels of insulin resistance, frequently get diabetes from exhaustion of the compensatory beta cells, but are shielded from fatty liver and atherogenic dyslipidemia. Patients with insulin receptor defects also exhibit elevated levels of adiponectin, IGFBP1, and SHBG, which are all typically suppressed in common insulin resistance or lipodystrophy-associated severe insulin resistance, which distinguishes them biochemically from individuals with other types of insulin resistance. This demonstrates the mechanisms underlying partial insulin resistance or post receptor selective defect in signalling through one arm of the insulin signalling pathway, both of which are frequently associated with obesity-related insulin resistance.

We have been able to determine the pathogenic relationship between the identified molecular flaw (or groups of faults) and obesity, early diabetes, or severe insulin resistance, each without the interference of the other components of the metabolic syndrome. In the future, we should keep looking for new monogenic causes for the remaining group of patients with severe disorders for which there is currently no known aetiology. This will not only help with their management but may also reveal potential novel and therapeutic targets for the metabolic syndrome, which is becoming more and more prevalent.

Conflict of Interest

The authors have no conflict of Interest

Acknowledgement

None

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Cite this article: Sabine Steffens. Metabolic Syndrome Pathogenesis: Evidence from Monogenic Disorders. J Diabetes Metab, 2022, 13(10): 958.