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REVIEW ARTICLE

Body Fat Distribution Contributes to Defining the Relationship between Insulin Resistance and Obesity in Human Diseases

María M. Adeva-Andany[1,*], Alberto Domínguez-Montero[1], Lucía Adeva-Contreras[2], Carlos Fernández-Fernández[1], Natalia Carneiro-Freire[1] and Manuel González-Lucán[1]

[1]*Nephrology Division, Department of Internal Medicine, Hospital General Juan Cardona, c/ Pardo Bazán s/n, 15406 Ferrol, Spain;* [2]*Medical School, Santiago de Compostela University, Santiago de Compostela, Spain*

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Abstract: The risk for metabolic and cardiovascular complications of obesity is defined by body fat distribution rather than global adiposity. Unlike subcutaneous fat, visceral fat (including hepatic steatosis) reflects insulin resistance and predicts type 2 diabetes and cardiovascular disease. In humans, available evidence indicates that the ability to store triglycerides in the subcutaneous adipose tissue reflects enhanced insulin sensitivity. Prospective studies document an association between larger subcutaneous fat mass at baseline and reduced incidence of impaired glucose tolerance. Case-control studies reveal an association between genetic predisposition to insulin resistance and a lower amount of subcutaneous adipose tissue. Human peroxisome proliferator-activated receptor-gamma (PPAR-γ) promotes subcutaneous adipocyte differentiation and subcutaneous fat deposition, improving insulin resistance and reducing visceral fat. Thiazolidinediones reproduce the effects of PPAR-γ activation and therefore increase the amount of subcutaneous fat while enhancing insulin sensitivity and reducing visceral fat. Partial or virtually complete lack of adipose tissue (lipodystrophy) is associated with insulin resistance and its clinical manifestations, including essential hypertension, hypertriglyceridemia, reduced HDL-c, type 2 diabetes, cardiovascular disease, and kidney disease. Patients with Prader Willi syndrome manifest severe subcutaneous obesity without insulin resistance. The impaired ability to accumulate fat in the subcutaneous adipose tissue may be due to deficient triglyceride synthesis, inadequate formation of lipid droplets, or defective adipocyte differentiation. Lean and obese humans develop insulin resistance when the capacity to store fat in the subcutaneous adipose tissue is exhausted and deposition of triglycerides is no longer attainable at that location. Existing adipocytes become large and reflect the presence of insulin resistance.

Keywords: Bardet Biedl syndrome, insulin sensitivity , lipodystrophy, cardiovascular disease, obesity, visceral fat.

1. INTRODUCTION

In humans, surplus energy is normally deposited as triglycerides in the subcutaneous adipose tissue to be used when exogenous food is in short supply. The capacity of subcutaneous adipose cells to store fat in response to excess energy is variable among individuals and reflects the degree of insulin sensitivity. Humans with a greater capacity to store triglycerides in the subcutaneous adipose tissue in response to caloric overload exhibit enhanced insulin sensitivity. Several lines of evidence support that notion and establish a connection between the ability to store fat in the subcutaneous adipose tissue and enhanced insulin sensitivity. First, a number of investigations document a positive association between greater subcutaneous adipose tissue mass and insulin sensitivity [1-4]. Second, human peroxisome proliferator-activated receptor-γ (PPAR-γ) is a transcription factor that promotes subcutaneous adipocyte differentiation and enhances insulin sensitivity, linking the ability to store fat in the subcutaneous adipose tissue with insulin sensitivity (Fig. **1**). The effects of PPAR-γ are highlighted by the clinical consequences of its congenital deficiency and by the effects of its exogenous agonists, the thiazolidinediones. PPAR-γ deficiency due to inactivating mutations in the *PPARG* gene cause loss of subcutaneous adipose tissue and insulin resistance [5-10], whereas thiazolidinediones replicate the effects of PPAR-γ and therefore facilitate subcutaneous fat deposition, improve insulin sensitivity, and decrease non-subcutaneous fat. Furthermore, the increase in subcutaneous fat 1 or the decrease in non-subcutaneous fat [11-14]. correlate with the improvement of insulin sensitivity elicited by thiazolidinediones, suggesting that the restoration of the capacity to store fat in the subcutaneous adipose tissue improves insulin resistance. Third, the clinical picture of human

*Address correspondence to this author at the Nephrology Division, Department of Internal Medicine, Hospital General Juan Cardona, c/ Pardo Bazán s/n, 15406 Ferrol, Spain; E-mail: madevaa@yahoo.com

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disorders such as lipodystrophy and Prader-Willi syndrome further highlights the connection between subcutaneous fat mass and insulin sensitivity. The lack of subcutaneous adipose tissue in patients with congenital lipodystrophy is associated with insulin resistance [15-22] while patients with Prader-Willi syndrome typically manifest pronounced subcutaneous obesity in the absence of insulin resistance, suggesting that the ability to store triglycerides in the subcutaneous adipose tissue associates with insulin sensitivity [23-25]. Fourth, multiple cross-sectional and prospective studies demonstrate an independent association between visceral fat and insulin resistance and establish that visceral fat precedes complications of insulin resistance, such as type 2 diabetes (T2D), [4, 26-29]. cardiovascular disease (CVD), [30-33] and kidney disease [34].

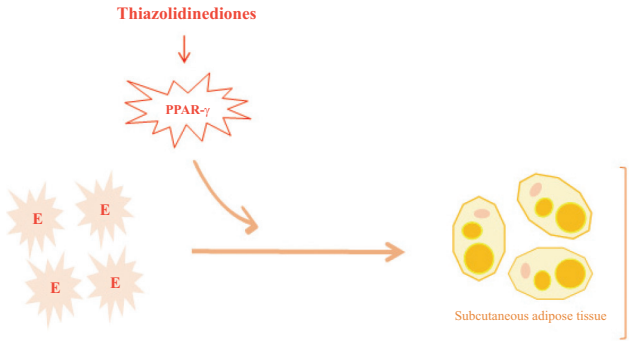

Fig. (1). Excess energy is normally stored in the subcutaneous adipose tissue as triglycerides. Peroxisome proliferator-activated receptor-gamma (PPAR-γ) facilitates this process. Thiazolidinediones are exogenous agonists of PPAR-γ. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

A restricted ability to store triglycerides in the subcutaneous adipose tissue is associated with insulin resistance and fat deposition in other locations following overfeeding, such as the intra-abdominal cavity (visceral fat), liver, skeletal muscle, or heart. Lean or obese humans develop insulin resistance (and visceral fat accumulation) whenever fat deposition in the subcutaneous adipose tissue is impaired [3, 35-39]. Causes that restrain fat accretion in the subcutaneous adipose tissue include deficient triglyceride synthesis, anomalous lipid droplet formation, and defective adipocyte differentiation. A limited capacity to store fat in the subcutaneous adipose tissue compromises the ability of this tissue to respond to surplus energy demand. Existing adipocytes enlarge to accommodate maximal lipid deposition and therefore large adipocytes become visible in the subcutaneous adipose tissue when no further triglyceride deposition is achievable. Subcutaneous adipocyte enlargement signals the presence of insulin resistance due to the exhausted capacity to store triglycerides. While adipocyte hypertrophy is observed in patients with insulin resistance, smaller subcutaneous adipocytes are identified in subjects with enhanced insulin sensitivity and unrestricted capacity to store subcutaneous fat. Cross-sectional studies indicate that large adipocytes are associated with insulin resistance [35, 37, 38, 40, 41], while prospective investigations establish that subcutaneous adipocyte hypertrophy precedes T2D in different population groups, regardless of body mass index (BMI) [35, 42]. Furthermore, larger subcutaneous adipocytes are present in young South Asians (mean age 27 years) compared to matched Caucasians, suggesting that South Asians have a lower capacity to store subcutaneous fat than Caucasians with similar age and BMI. In addition, adipocyte size correlated with insulin resistance (evaluated by hyperinsulinemic-euglycemic clamps), such that South Asian subjects demonstrated more pronounced insulin resistance than their Caucasian counterparts [43]. Likewise, the size of subcutaneous adipocytes is increased in patients with Alström syndrome compared to matched controls, confirming a status of more severe insulin resistance among Alström patients compared to controls [44].

In this review, we examined information available on the relationship between insulin resistance and obesity in human diseases highlighting the connection between the ability to store fat in the subcutaneous adipose tissue and insulin sensitivity. A comprehensive literature search was conducted on the PubMed database from its inception up to February 2023 that included articles containing the terms obesity, insulin resistance, diabetes, subcutaneous adipose tissue, visceral adipose tissue, fatty liver, hepatic steatosis, lipodystrophy, thiazolidinediones, PPAR-gamma, Prader-Willi syndrome, leptin, leptin receptor, pro-opiomelanocortin, melanocortin-4 receptor, insulin receptor, Bardet-Biedl syndrome, Alström syndrome, and other pertinent terms related with the relationship between insulin resistance and obesity in humans. Articles written in English concerning human subjects were included. Further relevant articles were identified by searching reference lists of the papers retrieved. Articles resulting from these searches were reviewed. At first, investigations on the association between visceral fat (as opposed to subcutaneous fat) and insulin resistance are reported. Then, the role of the PPAR-γ linking subcutaneous fat deposition and insulin sensitivity is considered, underscored by the effects of thiazolidinediones (exogenous PPAR-γ agonists) and PPAR-γ congenital deficiency. Next, human conditions that reveal an association between the ability to store fat in the subcutaneous adipose tissue and insulin sensitivity are described, including congenital lipodystrophy (absence of subcutaneous adipose tissue associates with insulin resistance) and Prader Willi syndrome (abundance of subcutaneous adipose tissue in absence of insulin resistance). Finally, the relationship between obesity and insulin resistance is analyzed in other congenital diseases, including Alström syndrome, Bardet Biedl syndrome (BBS), and mutations in the genes that encode leptin, leptin receptor, melanocortin-4 receptor (MC4R), and pro-opiomelanocortin (*POMC*).

2. VISCERAL FAT ASSOCIATES WITH INSULIN RESISTANCE AND CONSEQUENTLY PREDICTS TYPE 2 DIABETES AND CARDIOVASCULAR DISEASE WHILE THE ABILITY TO STORE SUBCUTANEOUS FAT REFLECTS INSULIN SENSITIVITY

It has been long known that general adiposity is not an optimal predictor for metabolic or cardiovascular complications of obesity. In 1956, Dr. Vague described two types of obesity based on the location of fat accumulation in the body. Abdominal obesity (reflecting excess visceral adipose tissue) was associated with T2D and premature atherosclerosis. In contrast, fat accumulation in the subcutaneous adipose tissue led to disorders proportional to the amount of fat, such as respiratory disease, orthopedic and locomotion difficul-

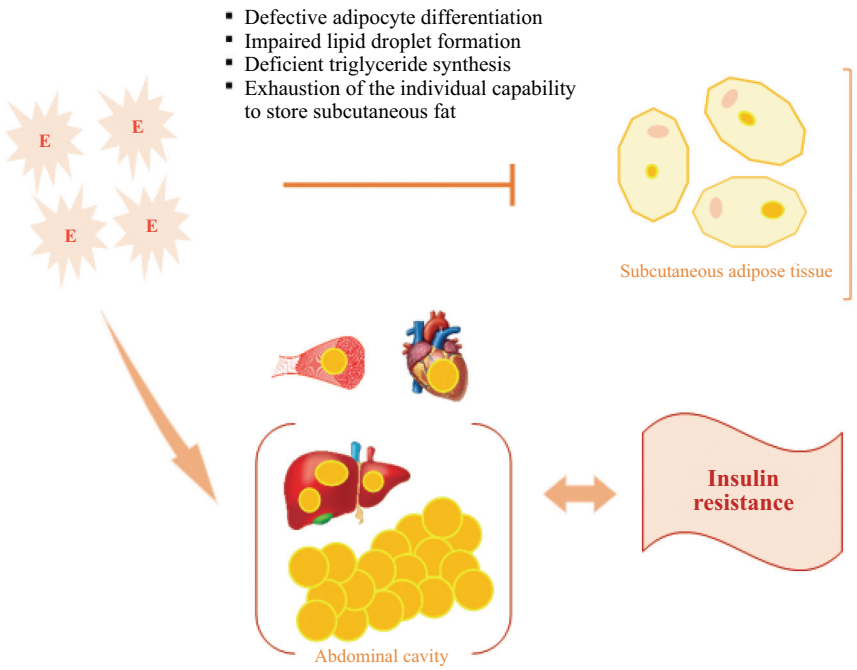

Fig. (2). Ectopic fat (including visceral fat and hepatic steatosis) is accumulated when subcutaneous fat accretion is impaired. Ectopic fat reflects insulin resistance. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

ties, and psychological and social burdens, but this form of obesity did not predispose to T2D or atherosclerotic CVD [45]. Multiple subsequent studies in humans have robustly confirmed this notion.

2.1. Excess Visceral Fat Reflects Insulin Resistance

As mentioned, individuals with limited ability to expand their subcutaneous fat in response to positive energy balance develop insulin resistance and visceral fat accretion following overfeeding (Fig. **2**). Cross-sectional and prospective trials establish that excess visceral fat (as opposed to subcutaneous fat) reflects insulin resistance and therefore precedes T2D and CVD in a variety of population groups, including non-obese subjects, obese patients, the elderly, patients with diabetes, and the general population. Initial investigations used waist circumference and waist-to-hip ratio to estimate visceral fat while subsequent studies evaluated body fat by ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), dual energy X-ray absorptiometry (DEXA), or bioimpedance. Cross-sectional studies uniformly reveal that visceral fat is independently and strongly associated with prevalent insulin resistance and components of the metabolic syndrome (the clinical expression of insulin resistance), in a variety of population groups, even in the absence of general adiposity and regardless of the way of assessment, either abdominal obesity [3, 46-49] or other procedures to evaluate body fat distribution [2, 41, 50-61]. Longitudinal studies establish that visceral fat at baseline predicts clinical consequences of insulin resistance at follow-up, such as T2D, CVD, and kidney disease. Prospective trials reveal that visceral fat precedes T2D, irrespective of the way of body fat assessment, either elevated waist-to-hip ratio [30-33] or visceral fat quantification [4, 26-29]. Subjects with increased visceral fat at baseline experience a higher risk of incident T2D at follow-up, regardless of BMI. In addition to T2D, prospective trial show that visceral fat predicts other clinical consequences of insulin resistance, such as CVD [30-33] and kidney disease [34]. A meta-analysis that included 40 observational studies confirmed that visceral fat mass is associated with insulin resistance, as measured by the homeostasis model assessment-insulin resistance (HOMA-IR) index [62].

In patients with T2D, similarly to other population groups, visceral fat is associated independently with insulin resistance or its clinical consequences (such as CVD including peripheral vascular disease and coronary artery disease), regardless of general obesity [63, 64].

In subjects with and without T2D, there is a strong correlation between visceral adipose tissue and liver fat content [56, 65]. Like visceral obesity, fatty liver (hepatic steatosis or non-alcoholic fatty liver disease) is associated with prevalent insulin resistance in both lean and obese subjects with [56, 65-67] and without [61, 68, 69] T2D. Furthermore, prospective studies reveal that hepatic steatosis at baseline increases the risk of incident T2D at follow-up. In a systematic review and meta-analysis that included a pooled population of 117,020 patients from 20 prospective studies with a median follow-up period of 5 years, hepatic steatosis (diagnosed by ultrasonography) was associated with an increased risk of incident T2D [70]. As a manifestation of insulin resistance, hepatic steatosis is associated with CVD [71, 72].

When the capacity of subcutaneous adipose tissue to store excess energy has been exhausted, fat accumulation may occur not only in the liver but also in other organs such as the heart, the skeletal muscle, and the pancreas. Like visceral fat and hepatic steatosis, excess pancreatic fat reflects the presence of insulin resistance. Pancreatic fat content correlates with visceral adipose tissue, liver fat accumulation,

HOMA-IR index, metabolic syndrome and bigger waist circumference [73-76]. Similarly to other population groups, pancreatic fat content is independently associated with insulin resistance (evaluated by the HOMA-IR index calculated with a formula using plasma level of C peptide) among patients with T2D [74]. In addition, pancreatic fat accumulation has been negatively associated with insulin secretion (assessed *via* oral glucose tolerance test-based measures or HOMA-β index) in subjects with impaired glucose tolerance or impaired fasting glycemia 73 and in male patients with T2D [74]. However, the association between pancreatic fat content and insulin secretion by β cells has not been identified in other investigations [75, 76]. In the skeletal muscle, intermuscular accumulation of fat may occur due to the inability of subcutaneous adipose tissue to store surplus triglycerides. Like visceral fat, this ectopic fat infiltration of the skeletal muscle (myosteatosis) reflects insulin resistance and consequently predicts the development of incident T2D in longitudinal studies [77]. However, myocytes contain triglycerides within intracellular lipid droplets to be used as a source of energy during exercise. Trained athletes show remarkable insulin sensitivity, but they have an elevated intramyocellular lipid pool as an adaptive response to training [78]. In the abdominal subcutaneous adipose tissue, the fascia superficialis separates two fat layers, deep and superficial. Cross-sectional studies have suggested that the amount of deep subcutaneous fat (unlike superficial) may correlate with fasting insulin level [79]. and insulin-stimulated glucose utilization, measured by euglycemic clamp [80]. Truncal fat is a correlate for visceral adiposity. Consequently, subjects with increased truncal fat experience a higher risk of metabolic syndrome [80, 81] and insulin resistance [82-84]. compared to individuals with normal truncal fat. As aging is associated with insulin resistance, a greater amount of truncal fat is observed at older ages in all ethnicities [85]. Sex differences have been identified in fat distribution, but they disappear after menopause. Before menopause, women typically show greater subcutaneous adipose tissue (peripheral fat) whereas men tend to accumulate abdominal (central) adipose tissue and visceral fat. For all ethnicities (Caucasian, African-American, Hispanic-American and Asian), men tend to exhibit more truncal fat than women [85]. Visceral fat area correlates with components of the metabolic syndrome independently of the menopause status, suggesting that the effect of menopause on the association between visceral fat and metabolic syndrome is not substantial [86].

2.2. Association between Subcutaneous Adipose Tissue and Insulin Sensitivity

As mentioned, the ability to store subcutaneous fat relates to insulin sensitivity. Cross-sectional, prospective, interventional, and genetic investigations find a positive association between subcutaneous adipose tissue mass and insulin sensitivity [1-4]. In a cross-sectional study that enrolled overweight or obese adults, the amount of subcutaneous adipose tissue, quantified by CT, was positively correlated with the degree of insulin sensitivity (evaluated by a modified insulin suppression test), despite similar BMI values [2]. In a prospective trial that followed South African women with normal glucose tolerance for 13 years, baseline subcutaneous fat mass, assessed by DEXA, was associated with reduced incidence of T2D or impaired glucose tolerance at follow-up, suggesting that subjects able to store more fat in the subcutaneous adipose tissue experience enhanced insulin sensitivity [4]. In patients treated with thiazolidinediones, the increase in subcutaneous fat [1] or the reduction in the ectopic lipid content in the skeletal muscle [11-14]. correlates with the improvement of insulin sensitivity elicited by these drugs. Accumulation of subcutaneous fat (as opposed to visceral fat) predicts the efficacy of troglitazone therapy in T2D patients, such that those with a greater increase of subcutaneous adipose tissue show better glycemic control than patients with lesser accumulation, suggesting that restoring the ability to store fat in the subcutaneous adipose tissue improves insulin resistance [1]. Further, large case-control studies reveal that genetic predisposition to insulin resistance is associated with lower amounts of subcutaneous adipose tissue. In a population-based investigation that included 188,577 participants in several trials (Fenland study, EPIC-Norfolk, EPIC-InterAct, UK Biobank, and the United Kingdom Household Longitudinal Study), genome-wide association analyses identified 53 loci associated with clinical features of insulin resistance. such as hyperinsulinemia, hypertriglyceridemia, and reduced HDL-c. Among 45,836 cases and 230,358 controls, the genetic predisposition to insulin resistance based on these 53 loci was associated not only with a higher risk of T2D and coronary heart disease (as expected) but also with lower subcutaneous adipose tissue mass. Furthermore, DEXA measures of body fat in 12,848 individuals showed that subjects with the highest genetic predisposition to insulin resistance had an average of 712 grams less leg fat mass (and higher risk of T2D) compared to individuals with the lowest genetic predisposition to insulin resistance [3].

3. HUMAN PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR-Γ ACTIVITY CONNECTS THE ABILITY TO STORE SUBCUTANEOUS FAT WITH INSULIN SENSITIVITY

Human PPAR-γ plays an important role in connecting subcutaneous fat deposition and insulin sensitivity by promoting adipocyte differentiation. Activation of PPAR-γ facilitates triglyceride deposition at a subcutaneous location and thus enhances insulin sensitivity and reduces visceral fat. The human *PPARG* gene codes two isoforms of PPAR-γ (PPAR-γ1 and PPAR-γ2) by differential promoter usage and alternate splicing. Human PPAR-γ is a transcription factor that modulates the transcription of target genes upon activation by a ligand. Endogenous ligands for PPAR-γ include 15-deoxy-δ-(12,14)-prostaglandin J2 while thiazolidinediones (such as troglitazone, rosiglitazone, and pioglitazone) are exogenous ligands. Upon ligand binding, PPAR-γ attaches to retinoid X receptors to create a heterodimer. In turn, the heterodimer PPAR-γ/retinoid X receptor binds to specific DNA sequences called PPAR-γ response elements in specific target genes to modulate gene transcription [87-92]. Human *PPARG* has a ubiquitous expression. PPARG1 is the predominant isoform while PPARG2 has a minor representation in human tissues. PPARG1 mRNA has been identified in human adipose tissue, large intestine (colon), small intestine, kidney, liver, heart, lung, endocrine pancreatic cells (α, β and δ islet cells), ovary, and placenta. Adipose tissue and large intestine have the highest levels while PPARG mRNA is

barely detectable in skeletal muscle. In contrast with the ubiquitous expression of PPARG1, human PPARG2 mRNA is only present in human adipose tissue. Even at that location, human PPARG2 mRNA is less abundant than PPARG1 in both visceral and subcutaneous adipose tissue [87-90, 92-95].

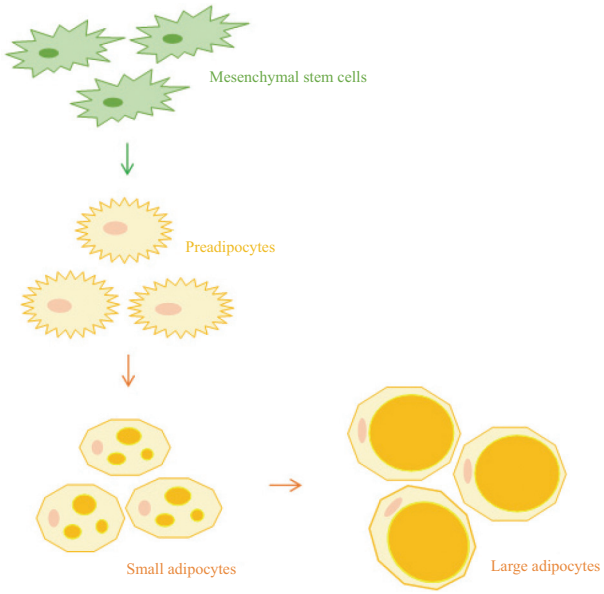

Fig. (3). Adipocyte differentiation. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

As mentioned, human PPAR-γ promotes adipocyte differentiation and consequently fat deposition in the subcutaneous adipose tissue. Human adipogenesis involves the commitment of mesenchymal precursors cells towards an adipose cell lineage (Fig. **3**). Then, mesenchymal stem cells undergo differentiation into preadipocytes which in turn differentiate into mature adipocytes. Both 15-deoxy-δ-(12,14)-prostaglandin J2 and thiazolidinediones enhance the differentiation of human preadipocytes isolated from subcutaneous depots, indicating the role of PPAR-γ favoring adipogenesis in the subcutaneous adipose tissue. In contrast, human preadipocytes from omental sites are refractory to the effect of thiazolidinediones [91].

Clinical studies reveal an association between defective subcutaneous adipogenesis and insulin resistance, suggesting that impaired adipocyte differentiation may contribute to the cause of insulin resistance. In patients with insulin resistance, subcutaneous adipose cells show an attenuated expression of genes involved in adipocyte differentiation (such as PPARG) [36, 96]. In addition, pioglitazone increases markers of adipocyte differentiation in subcutaneous adipose cells (such as adiponectin) and improves insulin sensitivity (assessed by hyperinsulinemic euglycemic clamp) [37].

The role of PPAR-γ coupling subcutaneous adipocyte differentiation with insulin sensitivity is highlighted by the clinical consequences that follow PPAR-γ congenital deficiency and by the effects of PPAR-γ agonists such as thiazolidinediones. Patients with congenital PPAR-γ deficiency manifest paucity of adipose tissue coupled with insulin resistance while thiazolidinediones promote subcutaneous fat accretion, enhance insulin sensitivity, and reduce visceral fat, as these drugs replicate the effects of PPAR-γ activation. Furthermore, the ability of PPAR-γ to enhance insulin sensitivity is underlined by the effect of interferons, which are components of the innate immune system that induce insulin resistance in response to infections. Interferons reduce the expression of the *PPARG* gene and suppress PPAR-γ activity, thus contributing to promoting insulin resistance during infections and other conditions associated with interferon upregulation, such as systemic lupus erythematosus.

3.1. Human Peroxisome Proliferator-activated Receptor-γ Genetic Variation

Heterozygous loss of function mutations in the *PPARG* gene causes *PPARG*-linked familial partial lipodystrophy (FPL) [5-10], whereas biallelic mutations in the *PPARG* gene have been reported to cause congenital generalized lipodystrophy (CGL) [97]. In addition to the absence of adipose tissue of variable extent, early presentation of profound insulin resistance and its clinical consequences (T2D, essential hypertension, hypertriglyceridemia, reduced HDL-c, polycystic ovary syndrome, and acanthosis nigricans) is typical. Relapsing pancreatitis associated with severe hypertriglyceridemia has been noticed [98-100]. Metreleptin, a synthetic analogue of human leptin, has been useful in patients with *PPARG*-linked FPL [100].

In addition to mutations in the *PPARG* gene, genetic variants in the *PPARG* gene in the general population may modulate the degree of insulin resistance (and therefore the predisposition to T2D) depending on their effect on PPAR-γ activity. Activating variants facilitate subcutaneous fat deposition and enhance insulin sensitivity while loss of function (inactivating) variants hinder subcutaneous fat accumulation, intensify insulin resistance and elevate the risk for T2D and visceral fat depots [101, 102].

3.2. Effects of Thiazolidinediones

Thiazolidinediones increase body weight but improve body fat distribution, as they promote subcutaneous fat deposition while reducing visceral fat. By increasing the capacity to store fat in the subcutaneous adipose tissue, thiazolidinediones enhance insulin sensitivity in subjects with and without T2D.

3.2.1. Thiazolidinediones Increase Subcutaneous Adipose Tissue and Reduce Visceral Fat

In patients with T2D, troglitazone [1, 11, 103-108]. and pioglitazone [13, 14, 109-114]. increase body weight and BMI but promote subcutaneous fat accumulation while reducing visceral fat depots, compared to placebo, diet, and other anti-diabetic medications. Accordingly, the increase in body weight in patients treated with thiazolidinediones is not accompanied by an increase in waist circumference. Likewise, these drugs improve body fat distribution (increasing subcutaneous fat while reducing visceral fat) in subjects without diabetes [12, 113, 115, 116].

3.2.2. Thiazolidinediones Improve Insulin Sensitivity and its Clinical Manifestations in Subjects with and Without Diabetes

Despite weight gain, troglitazone enhances insulin sensitivity in non-diabetic subjects [117]. and T2D patients. Additionally, troglitazone reduces fasting glucagonemia and glu-

cagon response to a meal tolerance test, compared to baseline values [11, 104, 107, 108, 118-120]. Both in T2D and non-diabetic subjects, troglitazone improves the clinical expression of insulin resistance, such that reduces triglyceride level [104, 107, 120] improves hepatic steatosis, [107] reduces skeletal muscle fat, [11] and decreases blood pressure [105, 115, 117]. Comparable effects are achieved by pioglitazone. In patients with and without T2D, pioglitazone improves insulin resistance [12, 14, 37, 109-111], decreases ectopic intramyocellular lipid content [12-14], reduces liver fat content [13, 110], diminishes serum triglyceride level and increases HDL-c [111, 112, 114].

3.3. Interferons Suppress PPAR-γ Expression and Induce Insulin Resistance

In addition to the genetic variations in the *PPARG* gene and the effects of PPAR-γ agonists, the crucial role of human PPAR-γ promoting insulin sensitivity is highlighted by the effect of interferon diminishing PPAR-γ expression.

Insulin resistance is a universal metabolic response to microbial invasion required to ensure energy availability to the activated immune system. Among other cytokines released in response to pathogens, interferons consistently induce insulin resistance in addition to their antimicrobial and antiproliferative effects [121, 122]. An increased expression of interferon-stimulated genes (interferon signature) is present in patients with infections and other conditions associated with insulin resistance compared to subjects with normal insulin sensitivity [123], Serum levels of both interferon and interferon correlates (neopterin and interferon-γ-inducible protein-10) are associated with insulin resistance. In addition, circulating levels of interferon-γ-inducible protein-10 are independently associated with the amount of visceral adipose tissue (but not that of subcutaneous fat), irrespective of BMI [124]. Furthermore, an increased level of type I interferon in visceral adipose tissue is positively associated with insulin resistance (evaluated by HOMA-IR) [123]. Accordingly, the abundance of immune cells producing interferon (such as macrophages) and interferon-γ transcript levels are higher in visceral fat compared to subcutaneous adipose tissue in obese subjects [125]. Additionally, recombinant type I interferon (interferon-α) induces a macrophage phenotype shift to enhance interferon production in the visceral adipose tissue of healthy subjects [123].

Human studies show that interferon diminishes the expression of PPAR-γ in adipocytes, suggesting that interferon may thus enable a reduction in the ability of subcutaneous adipocytes to store energy and subsequent insulin resistance [126, 127]. In adipose tissue obtained from obese subjects, interferon-γ reduces the expression of the *PPARG* gene [126]. *In vitro* studies using human adipocytes show that interferon-γ reduces PPAR-γ expression, suppresses preadipocyte differentiation into mature adipocytes, and reduces lipid droplet number and triglyceride content in mature adipocytes, compared to control cell lines [127]. Consistently, interferon-γ released by omental adipose tissue reduces the number of lipid droplets when incorporated into cultured human adipocytes. In an investigation that recruited obese patients with insulin resistance, omental fat was obtained and the explanted adipose tissue was cultured in the presence of macrophages and T cells. Human omental fat exposed to these immune stimuli releases interferon-γ that can be retrieved from the medium. When added to cultured human adipocytes, interferon-γ thus obtained decreases intracellular lipid droplet count and inhibits insulin action in the adipocytes [128].

In addition to its effect of decreasing PPAR-γ expression, human interferon markedly increases the expression of a lipid droplet protein, apolipoprotein L1 (APOL1) [129-134].

Human APOL1 is a component of the innate immune system that cooperate in the defense against microbial invasion and may mediate some effects of interferon. In addition to wild-type (normal) APOL1, two genetic variants of the protein have evolved in African American subjects that improve the protection against some infections (mainly human Trypanosomiasis), but also increase the risk for acute cellular rejection in kidney transplant recipients and contribute to cause some native kidney and vascular diseases [135, 136]. Disorders associated with APOL1 risk variants are usually triggered by excess interferon secretion. The intracellular location of APOL1 variants differs. While normal APOL1 is a component of the lipid droplet and contributes to lipid droplet formation, APOL1 risk variants are located in the endoplasmic reticulum and their absence from the lipid droplet prevents the formation of these intracellular organelles, suggesting that APOL1 risk variants promote insulin resistance [137, 138]. Excess interferon secretion upregulates the expression of APOL1, magnifies the defective formation of lipid droplets associated with the carriage of APOL1 risk variants, intensifies insulin resistance, and eventually triggers the appearance of the clinical phenotype associated with APOL1 risk variants. Clinical investigations confirm that carriers of APOL1 risk variants experience more clinical manifestations of insulin resistance compared to non-carriers [139-145]. Components of the metabolic syndrome, such as essential hypertension and obesity, develop more frequently in subjects harboring APOL1 risk variants compared to bearers of the wild type, suggesting that carriers of high-risk APOL1 genotype experience more severe insulin resistance than non-carriers [139, 140]. Kidney manifestations of insulin resistance (albuminuria, chronic kidney disease, and faster progression to end-stage kidney disease) are also more frequently encountered in subjects harboring APOL1 risk variants [141-145]. Likewise, histopathological manifestations of insulin resistance in the kidney such as increased glomerular size, focal segmental glomerulosclerosis, and arterionephrosclerosis are typically associated with APOL1 risk variants compared to wild type [146-148].

4. PRADER WILLI SYNDROME REPRESENTS A FORM OF SUBCUTANEOUS OBESITY UNLINKED TO INSULIN RESISTANCE

Prader-Willi syndrome (PWS) is a congenital disorder usually due to a deletion on the paternally derived chromosome 15q11-q13 region or to maternal uniparental disomy of the same region (15q11-q13). The defective protein or proteins that cause the clinical phenotype are unknown. During infancy, patients with PWS manifest hypotonia, poor feeding, failure to thrive, and underweight. Afterwards, they develop irrepressible hunger, lack of satiety, and hyperphagia

resulting in childhood obesity that persists into adulthood. In addition, growth hormone deficiency, short stature, hypogonadism, mental retardation, learning difficulties, and behavioral disturbances may develop. Clinical features of PWS have been attributed to hypothalamic dysfunction that can lead to growth hormone deficiency and overpowering appetite with subsequent hyperphagia [23, 149-153].

Obesity has been reported in 98% of PWS patients, but body composition differs in PWS patients compared to obese individuals with common multifactorial obesity or to normal weight subjects. In PWS patients, the percentage of lean mass (skeletal muscle) is lower compared to lean subjects and even more so compared to obese counterparts, as individuals with common obesity usually show increased lean mass compared to normal-weight subjects. Therefore, an abnormally high proportion of the body composition in PWS patients consists of adipose tissue at the expense of lean body mass and these patients show increased body fat compared to control subjects. Further, they experience a predominant accumulation of fat in the subcutaneous adipose tissue and reduced visceral fat, suggesting enhanced insulin sensitivity [24, 53, 149, 151-157]. Patients with longstanding isolated growth hormone deficiency manifest an abnormal body composition similar to that present in PWS patients (reduced lean mass and increased fat mass), suggesting that growth hormone deficiency contributes to the cause of this peculiar body composition. Accordingly, growth hormone therapy improves the abnormal pattern of body composition in both children and adult patients with PWS (increases skeletal muscle mass while reducing subcutaneous fat) with no adverse effects on glucose metabolism [158, 159]. Body composition in patients with PWS is already abnormal in infancy, before the development of childhood obesity. Infants with PWS are underweight and exhibit reduced arm circumference. Despite that, they show elevated triceps and subscapular skinfold thickness relative to BMI, suggesting relatively increased body fat in spite of being underweight. Accordingly, infants with PWS demonstrate increased percent body fat and decreased fat-free mass, assessed by DEXA and deuterium dilution technique, when compared to normal infants [149, 150].

Patients with PWS are severely obese but do not usually manifest insulin resistance. On the contrary, the pattern of fat distribution in PWS patients (fat accretion in the subcutaneous adipose tissue and reduced visceral fat) suggests enhanced insulin sensitivity, as mentioned. Furthermore, the rate of metabolic syndrome components and HOMA-IR values are consistently lower in both children and adults with PWS in comparison with matched controls [25, 153, 160-162]. Enhanced insulin sensitivity in PWS patients is confirmed by higher values of quantitative insulin sensitivity check index in PWS patients compared to obese controls with multifactorial obesity [23-25]. Moreover, plasma triglyceride and HDL-c levels are normal in PWS children, unlike obese controls [53, 160]. In addition, the prevalence of T2D is comparable in PWS patients and subjects from the general population, despite severe obesity in patients with PWS, although reported prevalence figures vary. In the general population, the prevalence of T2D is 13.0% of adults aged ≥ 18 years whereas in PWS patients the prevalence of T2D is 13.5%-13.7% in the larger studies, despite the presence of severe obesity [163, 164]. Enhanced insulin sensitivity in PWS patients does not fully protect them from developing diabetes due to a defect in insulin secretion. Case control studies consistently show that insulin levels (fasting and post-glucose load in oral glucose, mixed meal, and intravenous glucose stimulation) are lower in children and adult patients with PWS compared to matched control subjects. Deficient insulin secretion in PWS patients has been attributed to growth hormone deficiency of hypothalamic origin [23-25, 53, 153, 160, 162, 165, 166]. Like PWS patients, subjects with untreated long-standing isolated growth hormone deficiency manifest reduced insulin secretion and similar rate of diabetes compared to control subjects, suggesting that lifetime isolated growth hormone deficiency neither protect from the development of diabetes nor induce it [167, 168]. Consistently with the absence of insulin resistance despite severe obesity, atherosclerotic CVDs are not the primary causes of death in patients with PWS. The risk for all-cause mortality is higher in PWS patients *versus* the general population, with the median age at death being 30 years. Respiratory diseases are the predominant cause of death accounting for more than 50% of the deaths in children and adults with PWS. Mortality risk from respiratory failure has remained unchanged from years 2000 to 2015 in PWS patients. Cardiovascular deaths affected 14.4% individuals and included pulmonary embolism, cardiac tamponade, heart failure, and viral myocarditis while atherosclerotic CVD was not a predominant cause of death in patients with PWS [169-171].

5. CONGENITAL LIPODYSTROPHY: A SHORTAGE OF ADIPOSE TISSUE ASSOCIATED WITH INSULIN RESISTANCE AND ITS CLINICAL EXPRESSION

Lipodystrophies are a variety of congenital or acquired disorders characterized by partial or virtually complete loss of adipose tissue. A reduction in the amount of subcutaneous adipose tissue restricts fat accumulation at this location leading to insulin resistance and subsequent outcomes of insulin resistance such as T2D, essential hypertension, left ventricular hypertrophy, vascular disease, kidney disease (glomerular hyperfiltration and albuminuria), hypertriglyceridemia, reduced HDL-c, hyperuricemia, sarcopenia, lipolysis, hyperinsulinemia, polycystic ovary syndrome, acanthosis nigricans, and non-subcutaneous fat deposition including visceral fat and liver fat (hepatic steatosis) (Fig. **4**). Patients with generalized lipodystrophy show a widespread and uniform lack of adipose tissue and very low levels of circulating leptin (due to the systemic absence of adipose tissue). Patients with partial lipodystrophy exhibit reduced total body fat with a deficit of adipose tissue in some regions and preservation in others. Among them, plasma leptin is usually low but variable, depending on the total amount of adipose tissue. Recombinant methionyl human leptin (metreleptin) is a synthetic analog of human leptin that can be used to treat lipodystrophy. In patients with lipodystrophy and leptin deficiency, leptin replacement reduces hunger and enhances insulin sensitivity. Consequently, leptin therapy reduces serum triglyceride levels, lowers HOMA-IR, improves glycemic control in patients with lipodystrophy and T2D, diminishes hepatic steatosis, reduces glomerular hyperfiltration and proteinuria, lowers blood pressure and attenuates left ventricular hypertrophy

(due to insulin resistance-associated arterial stiffness). Leptin replacement is beneficial in patients with congenital generalized lipodystrophy while patients with partial lipodystrophy may show poor response to metreleptin, particularly when plasma leptin levels are not low [22, 172-179].

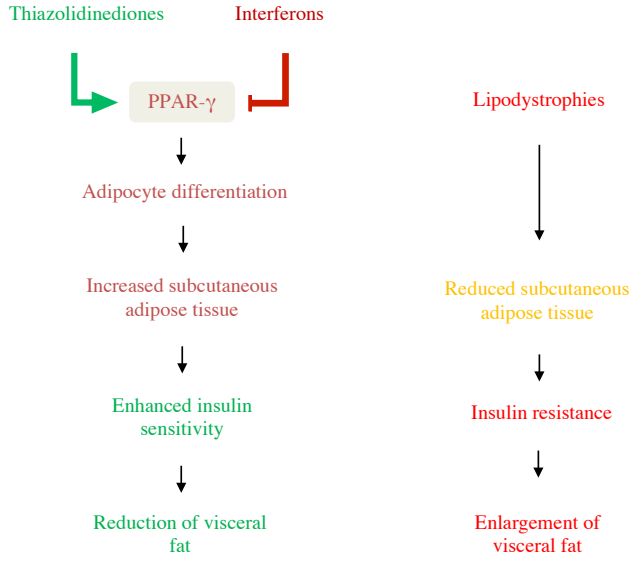

Fig. (4). Summary of the relationship between the amount of subcutaneous adipose tissue and insulin resistance in patients with lipodystrophy syndromes or receiving exogenous peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists (thiazolidinediones). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

5.1. Congenital Generalized Lipodystrophy

Congenital generalized lipodystrophies are inherited disorders characterized by the virtual absence of adipose tissue noticeable early in life, either from birth, infancy, or childhood. Patients endure insatiable appetite and subsequent overfeeding. In addition, they experience profound and premature insulin resistance and its clinical manifestations, such as T2D and hypertriglyceridemia that may lead to recurrent pancreatitis episodes. Other clinical features include accelerated growth, acromegaloid appearance with hands, feet, mandible, and genital enlargement, and advanced bone age during early childhood. Accordingly, with the lack of adipose tissue, serum leptin concentration is very low [18-20]. Life expectancy is shortened in patients with CGL, the predominant causes of death being infections (35%) and liver disease (35%) in a retrospective study that included 20 patients. Other causes of death included kidney failure, CVD, and acute pancreatitis. Three patients had pulmonary fibrosis [180]. Insulin resistance, assessed by glucose tolerance tests and euglycemic hyperinsulinemic clamps, is a universal finding in patients with CGL and the premature appearance of T2D is very common among these patients [15-22]. Plasma glucagon shows an exaggerated response to L-arginine [15]. Mutations in a number of genes including *AGPAT2*, *BSCL2*, *CAV1*, and *CAVIN1* cause CGL. In addition to the core characteristics of virtual lack of adipose tissue, severe insulin resistance and hypoleptinemia, patients with CGL manifest specific clinical features depending on the mutated gene causing the disease (Table **1**).

5.1.1. Acylglycerol-3-phosphate O-acyltransferase-2 (AGPAT2)-linked Congenital Generalized Lipodystrophy

In 1999, the first locus for CGL was mapped to human chromosome 9q34 and mutations in the *AGPAT2* gene (located at 9q34.3) were identified as the cause of the disorder in 2002. This gene encodes 1-acylglycerol-3-phosphate O-acyltransferase-2, the enzyme that catalyzes the formation of phosphatidic acid, thus contributing to triacylglycerol synthesis [18, 20]. Clinical features of severe insulin resistance such as left ventricular hypertrophy, CVD (coronary artery disease) and kidney disease may occur early in life [181].

5.1.2. Seipin-linked Congenital Generalized Lipodystrophy

Mutations in the *BSCL2* gene cause seipin-linked CGL (Berardinelli-Seip congenital lipodystrophy). This gene encodes seipin, a protein involved in the formation of lipid droplets and adipocyte differentiation. Nineteen Patients with seipin mutations usually show more severe clinical disease than patients with *AGPAT2* mutations do. The lack of adipose tissue is more pronounced and they have a loss of mechanical fat pads (such as palms and soles), unlike patients with *AGPAT2* mutations [181-183]. In addition, patients with *BSCL2* mutations have a higher prevalence of mild mental retardation and cardiomyopathy compared with *AGPAT2*-linked CGL [183]. Lytic lesions in long bones can be observed in both forms of CGL [183, 184].

5.1.3. Caveolin-1 (CAV1)-linked Congenital Generalized Lipodystrophy

Biallelic mutations in the *CAV1* gene cause CGL. This gene encodes caveolin-1, a component of caveolae (plasma membrane inlets) and lipid droplets [185]. Phenotypic peculiarities among patients with CAV1-linked FPL include pulmonary hypertension [186], achalasia, [187], retinitis pigmentosa, congenital cataracts, and neurological manifestations such as nystagmus, anomalous gait, and reduced strength [188]. In patients with homozygous *CAV1* mutations, MRI confirms near total absence of both subcutaneous and visceral adipose tissue [185].

5.1.4. Caveolae-associated Protein-1 (CAVIN1)-linked Congenital Generalized Lipodystrophy

Mutations in the *CAVIN1* (caveolae-associated protein-1) gene, also named PTRF (polymerase I and transcript release factor), cause CGL. CAVIN1 is a caveolar protein implicated in stabilizing caveolins to form caveolae [189]. In addition to generalized lipodystrophy, patients with *CAVIN1* mutations experience myopathy that may affect the heart muscle, skeletal muscle, and smooth muscle. They manifest muscle weakness and percussion-induced muscle contraction that produces muscle rippling. Smooth muscle hypertrophy in the gastrointestinal tract leading to impaired motility, dysphagia, ileus, and congenital pyloric stenosis has been observed. Hypertrophic cardiomyopathy, long QT and cardiac arrhythmias that may result in early sudden death have been reported. Other clinical features include atlanto-axial instability, impaired bone formation with osteopenia and osteoporosis, recurrent duodenal perforations, and increased susceptibility to infections. Serum creatine kinase levels are usually elevated [189-192]. Autopsy studies show a marked loss of subcutaneous and omental fat with fatty infiltration of the liver [193].

Table 1. Types of congenital generalized lipodystrophy (CGL).

Type / First Description	Gene / Chromosome Location	Protein	Protein Function	Differential Phenotype
AGPAT2-CGL (CGL1) Agarwal *et al.* 2002	*AGPAT2* / 9q34.3	1-acylglycerol-3-phosphate-acyltransferase-2	Triacylglycerol biosynthesis	Milder disease compared to seipin-CGL Bone lytic lesions (also reported in CGL2)
Seipin-CGL (CGL2) Magré *et al.* 2001	*BSCL2* / 11q13	Seipin (adipocyte differentiation factor)	Adipocyte differentiation / Lipid droplets generation	More serious disease than CGL1 Younger patients More severe lack of fat that includes "mechanical" pads Early diabetes Lower leptin levels Mental retardation Hypertrophic cardiomyopathy
***CAV1*-CGL (CGL3)** Kim *et al.* 2008	*CAV1* / 7q31.1	Caveolin-1 (CAV1)	Component of caveolae and lipid droplet	Pulmonary hypertension Achalasia Retinitis pigmentosa
***CAVIN1*-CGL (CGL4)** Hayashi *et al.* 2009	*PTRF* or *CAVIN1* / 17q21.2	Polymerase I and transcript release factor (PTRF), also named caveolae-associated protein-1 (CAVIN1)	Caveolae component involved in caveolae formation	Muscular dystrophy Skeletal muscle weakness Percussion-induced skeletal muscle rippling Elevated serum creatine kinase Long QT, cardiac arrhythmias, and sudden death Atlanto-axial instability Smooth muscle hypertrophy Hypertrophic cardiomyopathy Increased susceptibility to bacterial infections
FOS-CGL Knebel *et al.* 2013	c-FOS / 14q24.3	c-FOS	Transcription factor involved in adipocyte differentiation	Growth retardation Death at 8 years due to varicella infection
PPARG-CGL Dyment *et al.* 2014	*PPARG*	Peroxisome proliferator activated receptor-γ (PPAR-γ)	Adipocyte differentiation	Insulin resistance Kidney failure

5.1.5. Other Genes that may cause Congenital Generalized Lipodystrophy

As mentioned, biallelic mutations in the *PPARG* gene (that codes PPAR-γ) have been reported to cause CGL [97]. Mutations in the *C-FOS* gene have been associated with CGL and insulin resistance. The *C-FOS* gene encodes a transcription factor involved in cell proliferation and differentiation associated with the "immediate early response" after extracellular stimuli that participates in adipose tissue differentiation [194].

5.2. Familial Partial Lipodystrophy

Familial partial lipodystrophies are inherited conditions characterized by reduced total body fat with an anomalous distribution (lack of adipose tissue in some regions and preservation in other places). Patients with FPL typically experience insulin resistance and its clinical consequences. Mutations in a variety of genes may cause FPL. Depending on the mutated gene, patients with FPL show phenotypic peculiarities in addition to reduction of total body fat, abnormal allocation of adipose tissue, and insulin resistance [195] (Table **2**).

5.2.1. PPARG-linked Familial Partial Lipodystrophy

As mentioned, heterozygous mutations in the *PPARG* gene (that encodes PPAR-γ) cause FPL 5 while biallelic mutations cause CGL [97].

5.2.2. Mutations in Genes that Code the Insulin Receptor or Components of the Insulin Signaling Pathway cause Familial Partial Lipodystrophy

5.2.2.1. Mutations in the Insulin Receptor Gene

Biallelic (homozygous or compound heterozygous) mutations in the insulin receptor gene (*INSR*) cause Donohue syndrome or Rabson-Mendenhall syndrome while heterozygous mutations cause type A insulin resistance. The shortage of insulin receptors in the three diseases prevents insulin

Table 2. Types of familial partial lipodystrophy (FPL).

References	Type of FPL	Protein	Protein function	Differential phenotype
Kadowaki *et al.* 1990	Donohue syndrome Rabson-Mendenhall syndrome Type A insulin resistance	Insulin receptor	Insulin receptor	Defective insulin actions Early onset diabetes with fasting hypoglycemia and postprandial hyperglycemia Resistance to ketoacidosis Normal serum triglyceride level and normal liver fat
Speckman *et al.* 2000 Cao 2000	*LMNA*-linked FPL	Lamin A/C	Component of the nuclear lamina	Muscular dystrophy, cardiac manifestations, kidney failure, and other features
Agarwal *et al.* 2003	*ZMPSTE24*-linked FPL	Zinc metallo-proteinase STE24 (ZMPSTE24)	Cleavage of prelamin A	Mandibuloacral dysplasia: Clavicular and mandibular hypoplasia, short stature, and other manifestations
Barroso *et al.* 1999	*PPARG*-linked FLP	Peroxisome proliferator-activated receptor-γ	Subcutaneous adipose tissue adipogenesis	Early presentation of insulin resistance clinical features and lipodystrophy
Epstein *et al.* 1966	*WRN*-linked FPL	Werner protein	Maintenance of genome stability	Werner syndrome: short stature, dermopathy, predisposition to non-carcinomatous tumors, and other clinical features
Shastry *et al.* 2010	*POLD1*-linked FPL	DNA polymerase-δ1	Maintenance of genome stability / Prelamin A processing	Mandibular hypoplasia, sensorineural hearing loss, and other features
Bloom D. 1954	*BLM*-linked FPL	BLM helicase (RecQ DNA helicase)	Maintenance of genome stability	Bloom syndrome: Growth deficiency, predisposition to cancer, and other features
Graul-Neumann *et al.* 2010	*FBN1*-linked FPL	Asprosin	Increase of appetite	Undefined lipodystrophy and Marfan syndrome features

from exerting its actions creating a situation comparable to insulin deficiency (although an adaptive elevation in serum insulin levels takes place). In addition, these disorders are typically associated with a lack of adipose tissue of variable degree (partial lipodystrophy), suggesting that insulin signaling contributes to subcutaneous adipogenesis [196-199]. Similar to children with type 1 diabetes [200, 201], patients with mutations in the insulin receptor gene usually show normal liver fat and normal serum triglyceride and HDL-c levels [197-199]. Donohue syndrome (leprechaunism) and Rabson-Mendenhall syndrome have similar clinical characteristics but patients with Donohue syndrome endure a more severe phenotype with a high mortality rate before 2 years of age, the main cause of death being infections [197, 202-205]. As mentioned, insulin activity is very deficient in patients with these disorders and they consequently develop early-onset diabetes typically characterized by fasting hypoglycemia, postprandial hyperglycemia and resistance to ketoacidosis [197, 202-207]. Serum glucagon level is undetectable throughout mixed meal tests [205]. In addition, patients with Donohue syndrome and Rabson-Mendenhall syndrome demonstrate reduced subcutaneous adipose tissue and low skeletal muscle mass [202, 204, 205, 207, 208]. They typically suffer from intrauterine and postnatal growth retardation, reduced growth hormone and low weight at birth that remains usually low later in life [197, 202, 203, 205, 206]. Patients with Donohue syndrome may show gingival hypertrophy, kidney hypertrophy, hepatomegaly, enlarged genitals, hands and feet. Severe hypertrophic cardiomyopathy has been frequently reported among these patients [202, 205, 206, 208] (Table **3**).

Heterozygous mutations in the insulin receptor gene cause type A insulin resistance. The clinical phenotype is similar to that of biallelic mutations in *INSR*, but milder. Patients with type A insulin resistance manifest deficient insulin action and loss of subcutaneous adipose tissue. Most of them show low or normal weight and BMI [197, 199, 203, 209, 210]. Fat distribution examined by DEXA, abdominal CT, and MRI shows partial loss of subcutaneous fat in the abdomen, reduction of visceral fat, and absence of hepatic steatosis [199].

5.2.2.2. Mutations in Genes that Code Components of the Insulin Signaling Pathway

Like carriers of mutations in the insulin receptor gene, patients with mutations in *PIK3R1* and *AKT2* genes (that code components of the insulin signaling pathway) usually display a variable degree of lipodystrophy.

Phosphatidylinositol-3 kinase (PI3K) is a heterodimeric component of the insulin signaling cascade that possesses a 110-kDa catalytic subunit and an 85-kDa regulatory subunit or regulatory subunit-1 (PIK3R1). The *PIK3R1* gene codes the p85α regulatory subunit of PI3K [211]. In 2013, heterozygous mutations in the *PIK3R1* gene were identified as the cause of SHORT syndrome, which is clinically characterized

Table 3. Body fat distribution and insulin resistance in some human diseases and thiazolidinedione therapy.

-	Global Amount of Adipose Tissue	Subcutaneous Fat	Visceral Fat	Insulin Resistance	Main Therapy
Thiazolidinedione therapy	Increased	Increased	Decreased	Enhanced insulin sensitivity	-
Prader Willi syndrome	Increased	Increased	Normal	No	Lifestyle and nutritional interventions Growth hormone
Lipodystrophy	Reduced	Reduced	Usually increased	Severe insulin resistance	Metreleptin
Mutations in the leptin gene	Increased	Increased	Limited information	Limited information	Metreleptin
Mutations in the leptin receptor gene	Increased	Increased	Limited information	Limited information	Bariatric surgery Setmelanotide Methylphenidate
Mutations in the melanocortin-4 receptor gene	Increased	Increased	Limited information	Limited information	Bariatric surgery Setmelanotide
Mutations in the pro-opiomelanocortin gene	Increased	Increased	Limited information	Limited information	Setmelanotide Hydrocortisone

by intrauterine and postnatal growth retardation, low birth weight, short stature, inguinal hernia, hyperextensibility of joints, Rieger anomaly (anterior-chamber eye anomalies), delayed dentition, triangular face, small chin with a dimple, ocular depression (deep-set eyes), hearing loss, and delayed speech. Patients with SHORT syndrome typically manifest defective insulin action and loss of adipose tissue (lipodystrophy) [212-216].

Heterozygous mutations in the *AKT2* gene that encodes the kinase AKT2 (protein kinase B-β) have been reported to cause partial lipodystrophy, severe insulin resistance, and diabetes in only one pedigree [217]. Large case-control studies in British and Chinese population groups show that single nucleotide polymorphisms in the *AKT2* locus are not associated with T2D risk [218, 219].

5.2.3. Familial Partial Lipodystrophy Associated with Lamin A/C Deficiency (Mutations in the Genes LMNA and ZMPSTE24)

Lamins are intermediate filaments that participate in the structure of the nuclear lamina, a network located at the inner aspect of the nuclear membrane. The *LMNA* gene encodes (by alternative splicing) two major lamin isoforms, A and C, that differ in their C-terminal domain. Mature lamin A is derived from a precursor protein, prelamin A, through several post-translational modifications, including cleavage by the enzyme zinc metallopeptidase STE24 (ZMPSTE24). The enzyme DNA polymerase-δ1 (POLD1) has been also implicated in prelamin A processing and mutations in the gene that codes this enzyme also cause FPL [220]. Mutations in the *LMNA* gene cause a variety of diseases collectively named laminopathies that may affect skeletal muscle, cardiac muscle, heart conduction system, adipose tissue, and peripheral nerves and usually show overlapping clinical expression [221].

5.2.3.1. LMNA-linked Familial Partial Lipodystrophy

Patients with *LMNA*-linked FPL usually show normal fat distribution at birth and during childhood. After puberty, they experience loss of subcutaneous adipose tissue from the extremities and trunk while fat accumulates in the face and neck. They endure profound insulin resistance and therefore they may manifest complications of this metabolic alteration, including early cardiovascular events [221-223]. DEXA and MRI examinations reveal markedly diminished subcutaneous fat in the extremities with substantial fat deposition in other regions (neck and perinephric, retroperitoneal and intermuscular areas) compared to control subjects. MRI shows hepatic steatosis [224, 225]. Patients with *LMNA*-linked FPL have lower plasma levels of leptin compared with controls [226]. Post-mortem findings confirm an anomalous fat distribution with a paucity of subcutaneous fat in the extremities, accumulation of fat in the face and neck, excess visceral fat deposition, and extensive hepatic steatosis [227, 228].

Additionally, to partial lipodystrophy and insulin resistance, patients with LMNA mutations may show an array of skeletal muscle, nerve, and heart clinical manifestations, such as progressive muscular dystrophy with muscle weakness and myalgias, nerve entrapment syndromes, congestive heart failure, atrial fibrillation, dilated cardiomyopathy and conduction system disturbances such as atrioventricular block, arrhythmias, and sudden cardiac death. They may require defibrillator implantation or cardiac transplantation before 30 years of age [223, 229]. Kidney disease has been reported in patients with *LMNA*-linked FPL [230-233].

Both monoallelic and biallelic mutations in the *LMNA* gene may cause FPL. Biallelic mutations tend to cause more severe phenotypes than monoallelic (heterozygous) molecular changes. Homozygous patients exhibit more pronounced fat loss, more severe insulin resistance, earlier onset of insu-

lin resistance complications, and lower leptin level, compared to heterozygous patients [195, 234].

5.2.3.2. ZMPSTE24-linked Familiar Partial Lipodystrophy (Mandibuloacral Dysplasia)

Biallelic (compound heterozygous or homozygous) mutations in the *ZMPSTE24* (zinc metalloproteinase STE24) gene cause mandibuloacral dysplasia. As mentioned, this enzyme is involved in the post-translational cleavage of prelamin A to generate mature lamin A. Mutations in *ZMPSTE24* may impair prelamin A processing and reduce the formation of lamin A. Patients with mandibuloacral dysplasia may exhibit a broad spectrum of clinical manifestations including lipodystrophy. In a review of the patients reported until 2019, clinical features present in 85-100% of subjects were: short stature, delayed closure of cranial sutures, high palate, clavicular hypoplasia, mandibular hypoplasia, dental crowding, acro-osteolysis of the distal phalanges, hypoplastic nails, brittle and/or sparse hair, mottled pigmentation, atrophic skin similar to scleroderma, and calcified skin nodules. Clinical manifestations present in 70-84% of patients were lipodystrophy, shortened phalanges, and joint stiffness and contractures. Other phenotypic manifestations that have been reported include myopathy, arterial hypertension, heart failure, postnatal growth retardation, feeding difficulty, delayed dentition, teeth abnormalities, micrognathia, glomerular kidney disease (collapsing glomerulopathy and non-specified focal segmental glomerulosclerosis), end-stage kidney disease, enlarged fontanelles, recurrent bone fractures, underdeveloped occipital bone (ossification defect of the occipital bone), short phalanges of the hands, and premature birth. Lipodystrophy associated with mandibuloacral dysplasia is usually partial and shows a variable distribution that may affect the face, neck, trunk, or extremities. Loss of subcutaneous fat from palms and soles is a frequent finding. A slight increase of fat in the neck may occur [235, 236]. Oral glucose tolerance tests and insulin-stimulated glucose disposal procedures in patients with mandibuloacral dysplasia indicate that insulin resistance is usually present [237].

5.2.4. Familial Partial Lipodystrophy Caused by Mutations in Genes Involved in Genome Stability (Werner Syndrome, DNA Polymerase-δ1 Deficiency, and Bloom Syndrome)

5.2.4.1. WRN-linked Familial Partial Lipodystrophy (Werner Syndrome)

Biallelic mutations in the *WRN* gene cause Werner syndrome. The Werner protein operates both as a helicase (an enzyme that unwinds and separates double-stranded DNA) and an exonuclease (an enzyme that removes damaged DNA) and contributes to maintaining DNA structure and integrity by repairing damaged DNA, particularly at the ends of chromosomes (telomeres).

Werner syndrome is clinically characterized by partial lipodystrophy, severe insulin resistance (and its clinical manifestations), and a variety of other features that may include cataracts, short stature, scleroderma-like dermopathy with dermal fibrosis, atrophy of the skin and chronic ulcerations, premature loss and graying of the hair, and susceptibility to neoplasms (mainly non-carcinomatous). The life expectancy of patients with Werner disease is shortened, the two principal causes of death being malignancies and CVD [238, 239]. A systematic review that analyzed the risk and spectrum of neoplasia in 189 patients with Werner syndrome concluded that the disease is associated with an elevated risk of several specific types of neoplasia compared to the general population. The most frequent tumors (66.6%) in the Werner patients were thyroid neoplasms, malignant melanoma, meningioma, soft tissue sarcomas, leukemia and pre-leukemic conditions of the bone marrow, and primary bone neoplasms [240].

In patients with Werner syndrome, total body fat is diminished and there is an abnormal distribution of adipose tissue. Reduction of subcutaneous adipose tissue affects predominantly the limbs. Abdominal CT reveals increased visceral fat (intra-abdominal adipose tissue). Similar to other population groups, visceral fat deposition is strongly associated with insulin resistance in Werner syndrome patients [241-244].

Profound insulin resistance is a universal finding in patients with Werner disease, having been documented by euglycemic clamps, oral and intravenous glucose tolerance tests, intravenous glucagon administration, insulin sensitivity indexes, hyperinsulinemia and hypertriglyceridemia [243-251]. Elevated plasma glucagon levels and intensified glucagon response to a test meal have been observed in patients with Werner syndrome [241, 252]. Accordingly, body composition analyses by DEXA, CT, or bioelectrical impedance show reduced skeletal muscle mass consistent with the diagnosis of sarcopenia in patients with Werner syndrome. Sarcopenia is present even in younger patients aged < 40 years [253, 254].

Consistently with the presence of pronounced insulin resistance, the prevalence of abnormal glucose tolerance or T2D (62.2%) and CVD (24.3%) is high in patients with Werner syndrome. Like in other population groups, insulin resistance is closely related to vascular disease among Werner patients. Early-onset diabetes (in youth or early adulthood) is a common presentation of Werner syndrome and may appear before other features of the disease [243-251]. In patients with Werner syndrome and diabetes, pioglitazone enhances insulin sensitivity (assessed by the insulin sensitivity index) and elicits a striking improvement in metabolic control, with a reduction of fasting and post-prandial plasma glucose, serum insulin, and serum triglyceride level [243, 244]. Furthermore, pioglitazone improves body fat distribution among Werner patients, as they gain weight but the visceral fat area decreases while the subcutaneous fat mass increases [243].

5.2.4.2. POLD1-linked Familial Partial Lipodystrophy

The *POLD1* gene encodes DNA polymerase-δ1, the 125 kDa catalytic subunit of the DNA polymerase δ complex. This enzymatic complex is involved in DNA replication and DNA damage repair and contributes to maintaining genome stability. POLD1 contains an exonuclease domain and a polymerase domain and shows both exonuclease ($3' \longrightarrow 5'$) and polymerase activities. Heterozygous mutations in the *POLD1* gene may cause either predisposition to neoplasms (colorectal adenomatous polyps, colon cancer, endometrial cancer, breast cancer, and brain tumors) or a syndrome characterized by mandibular hypoplasia, sensorineural hearing loss, partial lipodystrophy, and insulin resistance.

It has been proposed that heterozygous mutations within the exonuclease domain of the *POLD1* gene cause a tumor-prone condition whereas heterozygous mutations within the polymerase domain cause *POLD1*-linked partial lipodystrophy associated with insulin resistance and other phenotypic manifestations [255-257].

The DNA polymerase δ complex and the Werner protein assembles into a multiprotein structure and cooperate to maintain genomic stability. The Werner protein stimulates the activity of the DNA polymerase δ complex, facilitating DNA synthesis and/or DNA repair [258, 259]. In addition, fibroblasts from patients with *POLD1* mutations exhibit an accumulation of prelamin A, suggesting that POLD1 may be involved in prelamin A processing. This notion is supported by overlapping clinical manifestations of POLD1 deficiency and lamin A deficiency [220].

Heterozygous mutations in the *POLD1* gene (polymerase domain) cause a syndrome with a broad spectrum of phenotypic manifestations that includes partial lipodystrophy and insulin resistance. Patients with *POLD1* mutations typically exhibit mandibular hypoplasia and bilateral sensorineural hearing impairment occurring during the first or second decade of life. In addition, patients with this disorder may show a wide spectrum of clinical features, including growth retardation, short stature, hypogonadism, prominent eyes and nose, dental crowding, scleroderma-like atrophic skin, telangiectasias, skin pigmentation, stiff joints, ligament contractures, hypogonadism, cryptorchidism, testicular atrophy, muscle cramps, hirsutism, osteopenia, thoracic kyphosis and scoliosis. Some patients have recurring respiratory infections that may become life-threatening [260, 261].

Regarding partial lipodystrophy and insulin resistance, patients with *POLD1* mutations usually have normal weight at birth but abnormal distribution of adipose tissue gradually takes place in childhood with loss of adipose tissue in face and limbs and visceral fat accumulation. DEXA scans, abdominal ultrasound, CT, MRI, and bioimpedance show a reduction of total fat mass, reduced subcutaneous adipose tissue in the face and limbs, reduced skeletal muscle mass, a marked increase in visceral fat, and hepatic steatosis. Liver biopsy may confirm non-alcoholic fatty liver disease. Serum leptin levels are usually low. In patients with *POLD1* mutations insulin resistance occurs despite low BMI values, having been evaluated by hyperinsulinemia, HOMA-IR values, oral glucose tolerance tests, and glucose clamps. Clinical expression of insulin resistance may include diabetes, essential hypertension, subclinical vascular disease, hypertriglyceridemia, reduced HDL-c, polycystic ovary syndrome, and acanthosis nigricans [220, 255, 256, 260, 262, 263]. Pioglitazone has improved insulin resistance and plasma hypoleptinemia in patients with *POLD1* mutations [263].

5.2.4.3. BLM-linked Familial Partial Lipodystrophy

Biallelic (homozygous or compound heterozygous) mutations in the *BLM* gene cause Bloom syndrome. The *BLM* gene encodes a RecQ DNA helicase. The absence of a functional BLM protein causes chromosome instability and an elevated rate of sister chromatid exchanges which is used as a marker of the syndrome by cytogenetic analysis [264, 265].

The typical phenotype of Bloom syndrome includes partial lipodystrophy, insulin resistance, microcephaly, prenatal and postnatal growth deficiency, short stature, feeding difficulties in infancy, sun-sensitive skin lesions (predominantly telangiectatic erythema), a variety of ocular manifestations (early onset of retinal drusen, conjunctival telangiectasia, optic nerve hypoplasia, and retinoblastoma), chronic lung disease, hypothyroidism, immunodeficiency, recurrent infections (usually respiratory or gastrointestinal), cancer predisposition and increased risk for the development of multiple cancers at a young age. The distribution of cancers is similar to the general population, but they occur at younger ages. Leukemia, lymphoma, and digestive tract cancers (particularly adenocarcinoma) occur commonly in patients with Bloom syndrome and earlier than the same tumors in persons from the general population [264-266].

Concerning lipodystrophy and insulin resistance, patients with Bloom syndrome show a paucity of adipose tissue and therefore low BMI [265]. Insulin resistance (and its clinical manifestations such as T2D and hypertriglyceridemia) is very frequent among these patients, being present from childhood [267].

5.2.5. Familial Partial Lipodystrophy Associated with Mutations in Other Genes

Mutations in several other genes, including *CAV1*, *LIPE*, *ADRA2A*, *CIDEC*, *PLIN1*, and *FBN1*, have been reported to cause FPL very rarely.

As mentioned, biallelic mutations in the *CAV1* gene (that codes caveloin-1) cause CGL. Heterozygous *CAV1* mutations have been reported to cause FPL and insulin resistance with hypertriglyceridemia and relapsing pancreatitis. In addition, congenital cataracts, retinitis pigmentosa, and neurological findings (nystagmus, anomalous gait, reduced power) may occur [188].

The genes *LIPE* [268]. and *ADRA2A* [269].encode hormone-sensitive lipase E and adrenoceptor α 2A, respectively. Both proteins have been implicated in lipolysis from adipocytes and mutations in these genes have been reported to cause FPL and insulin resistance.

The genes *CIDEC* and *PLIN1* code cell death-inducing DNA fragmentation factor-α-like effector C (CIDEC) and perilipin-1, respectively. CIDEC has been involved in lipid droplet formation [270-272] while perilipin-1 is a component of the lipid droplet envelope required for triglyceride incorporation and release from the droplet. Lipid droplets are cytoplasmic organelles that store triglycerides, being present predominantly in adipocytes [273, 274]. Mutations in *CIDEC* [270-272] and *PLIN1* [273, 274] genes have been reported to cause FPL and insulin resistance. However, the causal relationship between reported *PLIN1* gene mutations and FPL is unclear, as heterozygous mutations in *PLIN1* predicted to result in haploinsufficiency do not cause FPL. On the contrary, *PLIN1* haploinsufficiency may protect against cardiovascular disease by improving clinical features of insulin resistance. Subjects with *PLIN1* haploinsufficiency show reduced triglycerides, increased HDL-c, lower blood pressure, and reduced waist-to-hip ratio [275, 276].

Mutations in the *FBN1* gene may cause FPL. The product of the *FBN1* gene is profibrillin, a protein that undergoes post-translational processing to generate two different polypeptides, fibrillin-1 and asprosin, the latter being the result of the C-terminal cleavage of profibrillin. Asprosin is coded by exons located at the 3' end of the *FBN1* gene. This protein is released during fasting and promotes hunger and hepatic glucose production. Depending on the location of the molecular change, mutations in the *FBN1* gene may cause either typical Marfan syndrome (when the mutation affects fibrillin-1) or a variant of Marfan syndrome that includes congenital lipodystrophy, when the mutation induces dysfunction of asprosin. The total amount of body fat (determined by DEXA) is reduced in patients with mutations in the *FBN1* gene and Marfan variant, but other characteristics of the lipodystrophy have not been defined. Information on insulin sensitivity among these patients is limited, but plasma asprosin levels are correlated with insulin resistance and metabolic syndrome. Other phenotypic manifestations include severe myopia, bilateral lens subluxations, craniosynostosis, hydrocephaly and large head circumference, intrauterine growth retardation, premature birth, accelerated growth in height disproportionate to the scarce weight gain, tall stature, arachnodactyly, hyperextensible joints, aortic root dilatation, mitral valve prolapse, lumbosacral dural ectasia, pectus excavatum, and scoliosis [277-282].

6. INSULIN RESISTANCE IN SOME CONDITIONS ASSOCIATED WITH MONOGENIC OBESITY

Mutations in the leptin gene, the leptin receptor gene, the *MC4R* gene, and the *POMC* gene lead to early-onset uncontrollable hunger, overfeeding and severe obesity. The degree of insulin sensitivity in affected patients with these mutations is insufficiently known.

6.1 Mutations in the Genes that Code Leptin and the Leptin Receptor

In humans, serum leptin levels are variable among individuals and correlate with the total amount of body fat, such that circulating leptin is higher in obese subjects compared to non-obese individuals. In obese subjects, serum leptin level declines after weight loss [283-286]. In response to fasting, normal humans experience an acute and pronounced fall in serum leptin, regardless of the presence of obesity, that may serve to stir hunger sensation and compel the search for exogenous energy. Restoration of food intake is associated with a return to baseline leptin values. Leptin response to fasting is similar in lean and obese humans, as both of them experience a profound and comparable drop in serum leptin level after fasting. Serum leptin level decreases markedly following fasting compared to values prior to the fast in normal volunteers (lean, overweight, or obese). The striking decline in serum leptin does not correlate with the minuscule reduction in fat mass due to acute fasting, suggesting that acute leptin decline following fasting is independent of the amount of body adipose tissue [283, 287, 288]. Accordingly, serum leptin concentration tended to decrease in patients that received hypocaloric parenteral nutrition compared to total parenteral nutrition after surgical procedures [289]. Similarly, circulating leptin decreases during periods of negative energy balance in normal subjects. Long-term (7 days) energy restriction in normal-weight humans reduces circulating leptin [290]. Conversely, chronic overfeeding causes a rise in serum leptin that parallels the increase in the percentage of body fat in normal humans. There is a direct linear relationship between the magnitude of the leptin response and the percent gain of body fat [291].

6.1.1. Mutations in the Leptin Gene (Congenital Leptin deficiency)

Biallelic mutations in the gene encoding leptin (*LEP*) cause congenital leptin deficiency.

Patients affected with this condition show normal birth weight followed by rapid weight gain in the first few months of life due to constant hunger, impaired satiety and hyperphagia that lead to early-onset severe obesity. In addition, congenital leptin deficiency may be associated with impaired immune function (and increased susceptibility to infections), hypogonadotropic hypogonadism and hypothalamic hypothyroidism. Children with congenital leptin deficiency do not usually manifest growth retardation [292-298]. Plasma leptin level is usually very low (despite the markedly elevated fat mass), but some mutations in the leptin gene (c.298G→T; p.D100Y) may generate an inactive protein that circulates in plasma (resulting in high leptin levels) being biologically inoperative [299]. Body composition evaluation shows that congenital leptin deficiency is characterized by preferential deposition of fat mass [300, 301]. Information on the degree of insulin sensitivity in patients with mutations in the leptin gene is limited. Indirect indications of insulin resistance are commonly reported, including hyperinsulinemia, hypertriglyceridemia, reduced HDL-c, and non-alcoholic hepatic steatosis. Impaired glucose tolerance on oral glucose tolerance tests, high HOMA-IR values, and T2D have been documented in patients with congenital leptin deficiency, but the precise rate and magnitude of insulin resistance remain to be fully elucidated [292-294, 296-298, 301-308]. The administration of recombinant human leptin corrects the phenotypic anomalies associated with congenital leptin deficiency both in children and adults. The beneficial effects of leptin replacement include reduction of hunger, normalization of eating behavior, reduction in food intake, weight loss, fat mass reduction, amelioration of hypogonadism, hypothyroidism, and immune function, and improvement of insulin sensitivity and its clinical expression. Patients with T2D usually achieve glycemic control without additional therapy [294, 300, 302-304, 306, 307, 309]. Body composition evaluated by DEXA shows that body weight loss after leptin replacement is predominantly due to loss of fat, although a small decrease in fat-free body mass may occur that is substantially smaller than the loss of fat [294, 300, 303].

6.1.2. Mutations in the Leptin Receptor Gene

Biallelic mutations in the human leptin receptor gene (*LEPR*) cause deficiency of the leptin receptor and subsequent inability of leptin to exert its actions. In highly selected population groups of subjects with severe early-onset obesity, the prevalence of biallelic *LEPR* mutations ranges from 2.24% to 3% [310, 311]. The clinical phenotype of this condition is similar to that of mutations in the leptin gene. Affected patients manifest normal birth weight but they quickly gain weight in the first months of life due to constant

hunger, lack of satiety, and excessive eating that results in severe obesity. Patients with mutations in *LEPR* may also present hypogonadotropic hypogonadism, hypothalamic hypothyroidism (reduced secretion of thyrotropin), and alterations in the immune function that may lead to frequent childhood infections (predominantly recurrent respiratory infections). Clinical manifestations of insulin resistance have been documented, including hyperinsulinemia, HOMA-IR elevation, and T2D, but their frequency remains undefined. In subjects with *LEPR* mutations, serum leptin level is usually elevated, but it may be comparable to that observed in BMI-matched subjects [310-321]. Unlike patients with mutations in the leptin gene, leptin replacement is not beneficial in patients with mutations in the *LEPR* gene. Bariatric surgery procedures such as vertical ring gastroplasty [315, 319]. and drugs such as methylphenidate and setmelanotide (an agonist of the MC4R) have been used in patients with *LEPR* mutations with partial efficacy [322, 323].

6.2 .Mutations in the Melanocortin-4 receptor Gene (Melanocortin-4 Receptor Deficiency)

Pro-opiomelanocortin is a precursor protein that upon cleavage generates several melanocortin peptides, including adrenocorticotropic hormone (ACTH) and α -melanocyte-stimulating hormone (α-MSH), that mediate their physiological effects through specific G protein coupled receptors (melanocortin receptors) *via* activation of adenylyl cyclase and cyclic AMP signaling. ACTH stimulates melanocortin-2 receptors in the adrenal gland whereas α-MSH acts *via* the melanocortin-1 receptor in the skin and the MC4R in the hypothalamus. MC4R activation by α-MSH induces satiety and suppresses hunger [324] (Fig. **5**).

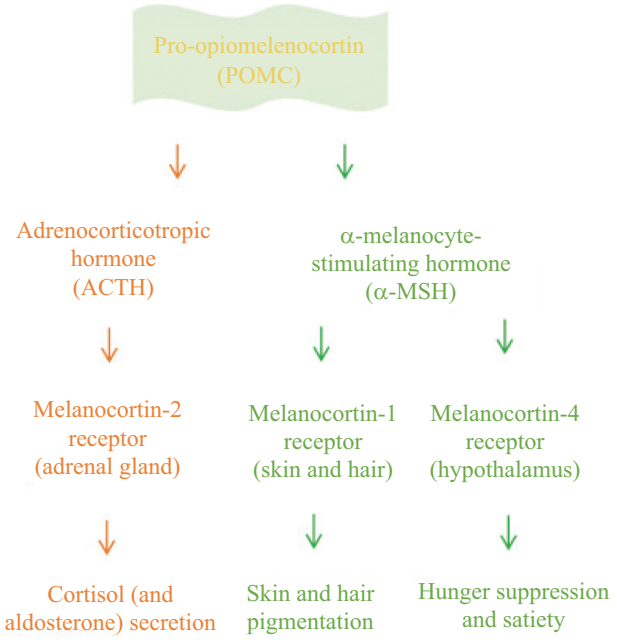

Fig. (5). Summary of human pro-opiomelanocortin derivatives and their effects. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Loss of function mutations in the human *MC4R* gene causes monogenic obesity due to irrepressible hunger and subsequent hyperphagia [325-328]. Most patients with congenital MC4R deficiency harbor heterozygous *MC4R* mutations, but probands with homozygous *MC4R* changes have been identified and they usually show more severe clinical phenotype compared to heterozygotes [327-331].

Patients with inactivating mutations in the *MC4R* gene manifest normal weight at birth but they develop persistent hunger and subsequent hyperphagia during the first months of life that leads to progressive weight gain and early-onset obesity. Obese patients with *MC4R* mutations tend to have tall stature. In a case control study that enrolled 153 heterozygous patients with MC4R deficiency and 1,392 matched controls, both heights during childhood and final adult height were higher in MC4R-deficient patients compared with controls. Common multifactorial childhood obesity is usually associated with increased linear growth, but a disproportionately accelerated linear growth is observed in patients with MC4R deficiency compared to obese controls [332, 333].

Patients with MC4R deficiency demonstrate obesity and elevated stature without other clinical peculiarities. Obesity is usually severe and develops early in life. Plasma leptin levels are high, as they reflect fat mass, but there is no difference between plasma leptin concentration in patients with MC4R deficiency and obese control subjects [334, 335].

The clinical phenotype of MC4R deficiency is more pronounced during childhood. In a longitudinal population-based study that evaluated 4,537 individuals, the slope of BMI increase was greater in individuals carrying an *MC4R* mutation compared with noncarriers during childhood but not during adulthood. Body mass accumulation was greatest during childhood but became similar to the rest of the population group after puberty [333]. The intense hunger sensation during childhood becomes less pronounced later in life and consequently, hyperphagia tends to be less prominent with progression into adulthood, suggesting that the effects of the *MC4R* mutations are more apparent during childhood [329, 333]. In patients with MC4R deficiency, DEXA studies show that both body fat mass and lean mass are increased, similar to subjects with common multifactorial obesity. Patients with MC4R deficiency are typically severely obese and tall, with increased fat-free mass as well as fat mass [329].

Information on the degree of insulin sensitivity is limited in patients with MC4R deficiency. Acanthosis nigricans has been reported in some patients with MC4R mutation. Fasting plasma insulin level has been found more elevated or similar to matched obese controls [328, 329, 334-336]. In prepubertal children with MC4R deficiency, plasma insulin concentration is greater compared with obese controls. However, the plasma insulin level is comparable to obese controls in adults with *MC4R* mutations [332]. Plasma triglyceride levels and HOMA-IR values are usually elevated in adult patients with MC4R deficits compared to non-obese control subjects. However, they are comparable to obese controls [334, 335].

Unlike adults, children with *MC4R* mutations experience a higher risk of developing T2D, independent of BMI and other covariates. Before the age of 20 years, a greater proportion of patients with MC4R deficiency developed T2D compared with control subjects (10.1% *versus* 2.6%), sup-

Table 4. Clinical commonalities and differences between Alström syndrome and Bardet Biedl syndrome.

Alström Syndrome	Bardet Biedl Syndrome
Retinal dystrophy and severe visual impairment Sensorineural hearing loss Intellectual disability Kidney disease Kidney and urinary tract structural anomalies Hypogonadism Fingers or toes defects (syndactyly, brachydactyly or polydactyly) Hepatic fibrosis Higher circulating leptin levels compared to BMI-matched control subjects	
Dilated cardiomyopathy	Cardiac malformations
Hypothyroidism	Anosmia
Normal height in children but short stature in adults	Short stature in children but normal height in adults
Childhood obesity that tends to normalize later in life	Frequent obesity
Severe early-onset insulin resistance and pronounced multiorgan fibrotic infiltration	Variable presence of mild insulin resistance

porting the notion that the effects of MC4R mutations are more conspicuous during childhood [333].

Patients with MC4R deficiency have been treated with bariatric surgery and setmelanotide (a MC4R agonist) [337-339].

In addition to inactivating mutations, variation in the *MC4R* gene may involve activating (gain of function) molecular changes that result in stimulation of the receptor with subsequent satiety and protection from obesity [334, 340, 341].

6.3. Pro-opiomelanocortin Mutations (*POMC* Deficiency)

In 1998, biallelic mutations in the *POMC* gene were reported to cause a distinct set of clinical findings that consisted of adrenal insufficiency, red hair, and early-onset obesity. *POMC* deficiency leads to impaired formation of both ACTH and α-MSH. ACTH deficit causes reduced cortisol synthesis while deficit of α-MSH causes obesity (due to diminished action of α-MSH on MC4R in the hypothalamus) and reduced skin and hair pigmentation (due to reduced activity of α-MSH activity on melanocytes) [324]. Subsequent reports confirmed the presence of this clinical picture. In patients with *POMC* mutations, ACTH deficiency and defective cortisol secretion are universally present and usually start during the neonatal period with hypoglycemic episodes, jaundice, and / or hypothermia. The birth weight is usually normal, but persistent hunger, reduced satiety and overfeeding lead to progressive obesity that begins to develop during infancy. Skin hypopigmentation and red hair may occur, but patients with congenital *POMC* deficiency may show normal hair and skin pigmentation, indicating that mutations in the *POMC* gene should be considered in subjects with isolated ACTH deficiency and hypocortisolism, particularly associated with early onset obesity. In addition, patients with *POMC* deficiency may manifest hypogonadotropic hypogonadism, hypothyroidism, and type 1 diabetes (14%), widening the initial clinical phenotype of the disorder [330, 342-354].

Information on the degree of insulin sensitivity in patients with *POMC* deficiency is very limited. Acanthosis nigricans has been diagnosed in some patients. Hepatic steatosis and hyperinsulinemia have been reported. In patients with type 1 diabetes and *POMC* mutations, insulin requirements have been noticed either similar or higher to type 1 diabetes patients without *POMC* mutations [349-351, 354].

Patients with *POMC* mutations should receive replacement therapy with hydrocortisone to correct adrenal insufficiency and thyroid hormone when hypothyroidism is present. In addition, some patients have been treated with metformin [351, 354] or setmelanotide [323].

Subjects with heterozygous mutations in the *POMC* gene (from kindreds of probands with biallelic *POMC* mutations and subsequent *POMC* deficiency) are usually overweight or obese compared to wild-type relatives [342, 355].

7. ALSTRÖM SYNDROME AND BARDET-BIEDL SYNDROME

The clinical phenotype of Alström syndrome and BBS share some commonalities, but it is different regarding insulin resistance and obesity. Alström syndrome is associated with early-onset severe insulin resistance and short stature in adulthood while patients with BBS are predominantly obese, with normal adult height and mild insulin resistance (Table **4**).

7.1. Alström Syndrome

Alström syndrome is an autosomal recessive disorder caused by mutations in the *ALMS1* gene. The ALMS1 protein is ubiquitously expressed in human tissues, having been detected in all tissues surveyed, including adipose tissue. Alternative splicing produces several isoforms of the protein [356]. In cultured human cell lines, ALMS1 localizes to the centrioles and the basal bodies (centriole-derived structures that participate in the formation of the cilium). ALMS1 is closely associated with γ-tubulin, a component of the pericentriolar material [356, 357]. In addition, human ALMS1 has been identified in the cytosol, outside the centrosome

[358]. The precise function of ALMS1 is unknown. It has been proposed that this protein may be implicated in the formation and maintenance of primary cilia, intracellular trafficking, microtubule and actin organization, cell adhesion, and extracellular matrix production [356]. *In vitro* studies using cultured human cell lines show that ALMS1 and some BBS proteins contribute to regulating Notch signaling by mediating the trafficking of this receptor toward the plasma membrane. In human embryonic kidney-293 cell lines, depletion of ALMS1, BBS1, BBS3, or BBS4 results in overactivation of Notch signaling, attributed to defective degradation of the Notch receptor [359].

Clinical manifestations of Alström syndrome appear during infancy and include retinal degeneration, severe visual impairment, sensorineural hearing loss, dilated cardiomyopathy, growth hormone deficiency, adulthood short stature, obesity, hypothyroidism, kidney disease, and hypergonadotropic hypogonadism in males. Severe early-onset insulin resistance is a hallmark of Alström syndrome. Similar to T2D, patients with Alström syndrome show profound multiorgan fibrotic infiltration [360-362].

Adult patients with Alström syndrome manifest uniformly short stature compared to control subjects [44, 360, 362-366]. Among 182 patients with this disorder, most children had rapid linear growth and obtained height above the 50th percentile before puberty. However, a progressive deceleration in linear growth is documented after puberty and the final adult height is below the 5th percentile [360]. Similar findings are obtained in a longitudinal investigation that followed 23 patients with Alström syndrome (age 1-52 years) for 10 years [366]. Growth hormone deficiency has been detected among adult patients with Alström syndrome [366].

Birth weight is within the normal range, but weight gain above normal is commonly observed during infancy and childhood in patients with Alström syndrome. After puberty, weight is comparable to controls and BMI tends to normalize in older individuals, suggesting that childhood obesity improves with age in patients with Alström syndrome [358, 360, 364-366]. In patients with this disorder, uncontrollable appetite and severe hyperphagia are not typically present, such that very high energy intake is not a definite determinant to obesity. Caregiver-reported hyperphagia and food intake records to evaluate overfeeding have yielded inconclusive results [358, 360, 362]. In patients with Alström syndrome, the total percentage of body fat (measured by DEXA) is similar to control subjects and the percent of body fat decreases with age. DEXA scans, abdominal CT, and MRI show that the distribution of adipose tissue is widespread both in subcutaneous and visceral locations [358, 362, 364, 367]. The level of serum leptin is higher in Alström syndrome patients compared to obese controls [44].

Patients with Alström syndrome show severe insulin resistance (assessed by HOMA-IR, quantitative insulin sensitivity check index, and hyperinsulinemic euglycemic clamps) that develops during early childhood. Therefore, the prevalence of T2D is strikingly high among these patients and the disease appears commonly during childhood or adolescence. Other clinical manifestations of insulin resistance are also typically present, including hyperinsulinemia, hepatic steatosis, vascular disease, essential hypertension, insulin resistance-related dyslipidemia (higher triglycerides and lower HDL-c). Elevated serum triglyceride level may precipitate pancreatitis [44, 358, 360, 362, 363, 365, 368]. Glucagon level after a mixed meal is higher compared to matched control subjects [362]. In contrast to obesity and body fat (that decrease with age), insulin resistance continues to worsen into adulthood in patients with Alström syndrome [358, 364]. Consistently with the presence of insulin resistance, Alström syndrome patients exhibit increased subcutaneous adipocyte size compared to obese controls. In a case-control study that enrolled 12 Alström patients and 11 obese control subjects with common polygenic obesity, subcutaneous adipocyte size was 6,033 ± 875 μm^2 in Alström participants *versus* 4,346 ± 880 μm^2 in obese control subjects [44].

7.2. Bardet-Biedl Syndrome

Bardet-Biedl syndrome is an autosomal recessive genetically heterogeneous disorder. Mutations in more than 20 genes have been reported to cause BBS up to now. *BBS10* and *BBS1* are the most frequently mutated genes followed by *BBS2* while mutations in the *BBS4* and *BBS9* genes are less frequent [369, 370]. Some (eight so far) BBS proteins assemble into a multiprotein complex. Other BBS proteins are thought to be chaperonin-like, as they display sequence homology with the CCT (chaperonin-containing tailless complex polypeptide 1). The function of human BBS proteins remains to be fully elucidated. They have been implicated in the trafficking of proteins including receptors (such as insulin receptor and leptin receptor) toward the plasma membrane and the cilium [369]. Some human BBS proteins may be involved in the formation of a primary cilium that appears transitorily in preadipocytes during human adipocyte differentiation. While mature adipocytes are non-ciliated cells, a primary cilium is transiently observed in differentiating preadipocytes. Upregulation of BBS6, BBS10, and BBS12 proteins (located to the basal body) is detected in ciliated preadipocytes [371]. In addition, the knockdown of any of these BBS proteins results in a decreased number of ciliated cells compared to control cultures, suggesting that they may be involved in the formation of the primary cilium during adipogenic differentiation of human mesenchymal stem cells [372]. Further, the inactivation of *BBS10* or *BBS12* genes in differentiating preadipocytes upregulates adipogenic genes such as *PPARG* and induces nuclear accumulation of PPAR-γ compared to control cells, suggesting adipogenesis activation in the BBS-depleted preadipocytes [371]. Accordingly, cultured adipocytes developed from BBS patients with mutations in the *BBS10* or *BBS12* genes exhibiting higher fat accumulation compared to control adipocytes with wild-type proteins. The leptin level secreted in the culture medium is higher in the BBS mutated cells compared to the control cells, consistently with the high circulating leptin in patients with BBS [371, 372]. Similarly, gene-expression analysis of adipose tissue from patients with BBS demonstrated increased expression of genes involved in adipogenesis, such as *PPARG*, compared to controls [372].

The phenotypic expression of mutations in the *BBS* genes includes retinal dystrophy that usually leads to blindness, finger anomalies (syndactyly, brachydactyly or polydactyly), obesity, intellectual disability (cognitive impairment, learning difficulties or mental retardation), hearing loss, cardiac malformations,

urogenital tract and kidney structural defects, kidney failure, hypogonadism, reproductive abnormalities or infertility, childhood onset asthma, and hepatic fibrosis [369, 373-381].

Unlike patients with Alström syndrome, children with BBS are shorter than control subjects while adults with BBS show similar stature compared to control individuals [370, 382]. Obesity is a common finding in patients with BBS. Birth weight is usually within the normal range, but most patients with BBS develop overweight or obesity during childhood which is sustained through adulthood [370, 373, 375, 383]. The total percent of body fat assessed by DEXA is similar in patients with BBS and BMI-matched controls [370, 384]. The cause of obesity in patients with BBS is unclear. Constant hunger and severe overfeeding do not typically occur in patients with BBS. Small case-control studies show inconclusive results regarding hyperphagia and energy intake [382, 384]. Like Alström syndrome, BBS patients have higher circulating leptin than expected for their degree of adiposity, as serum leptin levels are higher in patients with BBS compared to BMI-matched controls [370].

Unlike patients with Alström syndrome, severe insulin resistance is uncommon in patients with BBS. The degree of insulin sensitivity is variable and insulin resistance, when present, is mild [369, 370, 373, 376, 377, 381, 383]. The rate of clinical manifestations of insulin resistance, such as increased visceral fat [370, 373, 375]. and metabolic syndrome components (hyperinsulinemia, hypertriglyceridemia, and essential hypertension) [370, 383] has been reported higher in BBS patients compared to controls. HOMA-IR values are slightly higher in patients with BBS compared to controls but they show extensive overlap between the two groups [370, 383] and the prevalence of impaired glucose tolerance is similar for subjects with BBS and BMI-matched controls [370, 372] The rate of T2D among BBS patients varies markedly between studies, from 2% in younger patients (mean age 15 years) [370] to 48% in BBS patients from Newfoundland (median age 44 years) [385]. In Newfoundland, the high diabetes rate is comparable among subjects with (48%) and without (45%) mutations in the BBS genes [386]. Other T2D prevalence estimates that have been reported in patients with BBS include 15.8% (mean age 33.2 years) [383]. and 6% (mean age 26.3 years) [387]. In a study that enrolled 16 obese patients with BBS, histological examination of subcutaneous adipose tissue demonstrated similar adipocyte cell size (mean diameter of 100 μm) compared to control subjects with similar BMI, suggesting the absence of severe insulin resistance [372]. A correlation between BBS genotype and the degree of insulin resistance has been documented. BBS patients with mutations in the *BBS10* 370 or *BBS9* 381 genes show more severe insulin resistance than carriers of *BBS1* mutations.

Among individuals without BBS, genetic variation in *BBS* genes may be associated with obesity, metabolic syndrome traits, and T2D [378, 388, 389]. Case control studies find an association between single nucleotide polymorphisms in *BBS2*, *BBS4*, and *BBS6* genes and hypertriglyceridemia, hypertension, impaired glucose tolerance, and T2D [378, 388]. Genetic variants in *BBS1* and *BBS9* have been associated with obesity [389]. The homozygous carriage of a variant in the *BBS10* gene (c.1189A>G [p.Ile397Val].; rs202042386) confers increased risk for T2D [380].

CONCLUSION

In humans, unused energy is normally stored in the subcutaneous adipose tissue as fat. The ability to accumulate triglycerides at that location is variable among individuals, being partly genetically determined. Defective adipocyte differentiation, impaired lipid droplet formation, or deficient synthesis of triglycerides compromise the ability of subcutaneous adipose tissue to store fat. A restricted capacity to store fat in the subcutaneous adipose tissue elicits insulin resistance. Both lean and obese humans develop insulin resistance when the capacity to store fat in the subcutaneous adipose tissue has been exhausted. Subcutaneous adipocytes appear enlarged when their maximal capacity to store fat has been reached and no further triglycerides can be deposited. These large subcutaneous adipocytes reflect the presence of insulin resistance and consequently predict type 2 diabetes and cardiovascular disease. Surplus energy due to overfeeding is then deposited in places outside the subcutaneous adipose tissue, such as the abdominal cavity (visceral fat), the liver, the skeletal muscle, and the heart, as triglycerides cannot be accumulated as subcutaneous fat. Therefore, like large adipocytes, excess visceral fat reflects insulin resistance and predicts type 2 diabetes and cardiovascular diseases. In contrast, unrestricted capacity to store fat in the subcutaneous adipose tissue reflects enhanced insulin sensitivity. The connection between subcutaneous fat accretion and insulin sensitivity is underscored by the effects of human PPAR-γ, a transcription factor that promotes subcutaneous adipocyte differentiation, subcutaneous fat deposition, insulin sensitivity and reduction of visceral fat. Consistently, congenital PPAR-γ deficiency due to loss of function mutations in the *PPARG* gene leads to the absence of subcutaneous adipose tissue and insulin resistance while PPAR-γ agonists like thiazolidinediones increase subcutaneous adipose tissue, enhance insulin sensitivity and reduce visceral fat. These drugs increase body weight but improve body fat distribution by promoting subcutaneous fat accretion, thus improving insulin resistance. The link between the capacity to store fat in the subcutaneous adipose tissue and insulin sensitivity is further highlighted by case-control studies that show an association between genetic predisposition to insulin resistance and lower subcutaneous fat mass and by prospective studies that reveal a relationship between larger amounts of subcutaneous adipose tissue at baseline and reduced incidence of impaired glucose tolerance at follow-up. Additionally, numerous clinical studies establish an association between excess visceral fat or hepatic steatosis and insulin resistance. Furthermore, patients with a congenital lack of subcutaneous adipose tissue (congenital lipodystrophies) manifest insulin resistance whereas, on the opposite end of the clinical spectrum, patients with Prader-Willi syndrome experience severe subcutaneous obesity in the absence of insulin resistance.

LIST OF ABBREVIATIONS

ACTH	=	Adrenocorticotropic Hormone
α-MSH	=	α-melanocyte-stimulating Hormone
APOL1	=	Apolipoprotein L1
BBS	=	Bardet Biedl Syndrome
BMI	=	Body Mass Index

CT	=	Computed Tomography
CGL	=	Congenital Generalized Lipodystrophy
DEXA	=	Dual Energy X-ray Absorptiometry
FPL	=	Familial Partial Lipodystrophy
HOMA-IR	=	Homeostasis Model Assessment-insulin Resistance
MCR4	=	Melanocortin-4 Receptor
MRI	=	Magnetic Resonance Imaging
PI3K	=	Phosphatidylinositol-3 Kinase
POLD1	=	DNA Polymerase-δ1
POMC	=	Pro-opiomelanocortin
PPAR-γ	=	Peroxisome Proliferator-activated Receptor-gamma
PWS	=	Prader Willi Syndrome
T2D	=	Type 2 Diabetes

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REFERENCES

[1] Akazawa S, Sun F, Ito M, Kawasaki E, Eguchi K. Efficacy of troglitazone on body fat distribution in type 2 diabetes. Diabetes Care 2000; 23(8): 1067-71. http://dx.doi.org/10.2337/diacare.23.8.1067 PMID: 10937499

[2] McLaughlin T, Lamendola C, Liu A, Abbasi F. Preferential fat deposition in subcutaneous *versus* visceral depots is associated with insulin sensitivity. J Clin Endocrinol Metab 2011; 96(11): E1756-60. http://dx.doi.org/10.1210/jc.2011-0615 PMID: 21865361

[3] Lotta LA, Gulati P, Day FR, *et al.* Integrative genomic analysis implicates limited peripheral adipose storage capacity in the pathogenesis of human insulin resistance. Nat Genet 2017; 49(1): 17-26. http://dx.doi.org/10.1038/ng.3714 PMID: 27841877

[4] Mtintsilana A, Micklesfield LK, Chorell E, Olsson T, Goedecke JH. Fat redistribution and accumulation of visceral adipose tissue predicts type 2 diabetes risk in middle-aged black South African women: A 13-year longitudinal study. Nutr Diabetes 2019; 9(1): 12. http://dx.doi.org/10.1038/s41387-019-0079-8 PMID: 30918247

[5] Barroso I, Gurnell M, Crowley VEF, *et al.* Dominant negative mutations in human PPARγ associated with severe insulin resistance, diabetes mellitus and hypertension. Nature 1999; 402(6764): 880-3. http://dx.doi.org/10.1038/47254 PMID: 10622252

[6] Agarwal AK, Garg A. A novel heterozygous mutation in peroxisome proliferator-activated receptor-gamma gene in a patient with familial partial lipodystrophy. J Clin Endocrinol Metab 2002; 87(1): 408-11. http://dx.doi.org/10.1210/jcem.87.1.8290 PMID: 11788685

[7] Hegele RA, Cao H, Frankowski C, Mathews ST, Leff T. *PPARG* F388L, a transactivation-deficient mutant, in familial partial lipodystrophy. Diabetes 2002; 51(12): 3586-90. http://dx.doi.org/10.2337/diabetes.51.12.3586 PMID: 12453919

[8] Savage DB, Tan GD, Acerini CL, *et al.* Human metabolic syndrome resulting from dominant-negative mutations in the nuclear receptor peroxisome proliferator-activated receptor-gamma. Diabetes 2003; 52(4): 910-7. http://dx.doi.org/10.2337/diabetes.52.4.910 PMID: 12663460

[9] Agostini M, Schoenmakers E, Mitchell C, *et al.* Non-DNA binding, dominant-negative, human PPARγ mutations cause lipodystrophic insulin resistance. Cell Metab 2006; 4(4): 303-11. http://dx.doi.org/10.1016/j.cmet.2006.09.003 PMID: 17011503

[10] Campeau PM, Astapova O, Martins R, *et al.* Clinical and molecular characterization of a severe form of partial lipodystrophy expanding the phenotype of PPARγ deficiency. J Lipid Res 2012; 53(9): 1968-78. http://dx.doi.org/10.1194/jlr.P025437 PMID: 22750678

[11] Mathieu-Costello O, Kong A, Ciaraldi TP, *et al.* Regulation of skeletal muscle morphology in type 2 diabetic subjects by troglitazone and metformin: Relationship to glucose disposal. Metabolism 2003; 52(5): 540-6. http://dx.doi.org/10.1053/meta.2002.50108 PMID: 12759881

[12] Rasouli N, Raue U, Miles LM, *et al.* Pioglitazone improves insulin sensitivity through reduction in muscle lipid and redistribution of lipid into adipose tissue. Am J Physiol Endocrinol Metab 2005; 288(5): E930-4. http://dx.doi.org/10.1152/ajpendo.00522.2004 PMID: 15632102

[13] Teranishi T, Ohara T, Maeda K, *et al.* Effects of pioglitazone and metformin on intracellular lipid content in liver and skeletal muscle of individuals with type 2 diabetes mellitus. Metabolism 2007; 56(10): 1418-24. http://dx.doi.org/10.1016/j.metabol.2007.06.005 PMID: 17884455

[14] Bajaj M, Baig R, Suraamornkul S, *et al.* Effects of pioglitazone on intramyocellular fat metabolism in patients with type 2 diabetes mellitus. J Clin Endocrinol Metab 2010; 95(4): 1916-23. http://dx.doi.org/10.1210/jc.2009-0911 PMID: 20157197

[15] Kodama S, Kasuga M, Seki A, *et al.* Congenital generalized lipodystrophy with insulin-resistant diabetes. Eur J Pediatr 1978; 127(2): 111-9. http://dx.doi.org/10.1007/BF00445766 PMID: 203464

[16] Tsukahara H, Kikuchi K, Kuzuya H, *et al.* Insulin resistance in a boy with congenital generalized lipodystrophy. Pediatr Res 1988; 24(6): 668-72. http://dx.doi.org/10.1203/00006450-198812000-00003 PMID: 3060827

[17] Søvik O, Vestergaard H, Trygstad O, Pedersen O. Studies of insulin resistance in congenital generalized lipodystrophy. Acta Paediatr 1996; 85(s413): 29-38. http://dx.doi.org/10.1111/j.1651-2227.1996.tb14263.x PMID: 8783770

[18] Garg A, Wilson R, Barnes R, *et al.* A gene for congenital generalized lipodystrophy maps to human chromosome 9q34. J Clin Endocrinol Metab 1999; 84(9): 3390-4. http://dx.doi.org/10.1210/jcem.84.9.6103 PMID: 10487716

[19] Magré J, Delépine M, Khallouf E, *et al.* Identification of the gene altered in Berardinelli–Seip congenital lipodystrophy on chromosome 11q13. Nat Genet 2001; 28(4): 365-70. http://dx.doi.org/10.1038/ng585 PMID: 11479539

[20] Agarwal AK, Arioglu E, de Almeida S, *et al.* AGPAT2 is mutated in congenital generalized lipodystrophy linked to chromosome 9q34. Nat Genet 2002; 31(1): 21-3. http://dx.doi.org/10.1038/ng880 PMID: 11967537

[21] Petersen KF, Oral EA, Dufour S, *et al.* Leptin reverses insulin resistance and hepatic steatosis in patients with severe lipodystrophy. J Clin Invest 2002; 109(10): 1345-50. http://dx.doi.org/10.1172/JCI0215001 PMID: 12021250

[22] Javor ED, Moran SA, Young JR, *et al.* Proteinuric nephropathy in acquired and congenital generalized lipodystrophy: Baseline characteristics and course during recombinant leptin therapy. J Clin Endocrinol Metab 2004; 89(7): 3199-207. http://dx.doi.org/10.1210/jc.2003-032140 PMID: 15240593

[23] Talebizadeh Z, Butler MG. Insulin resistance and obesity-related factors in Prader-Willi syndrome: Comparison with obese subjects. Clin Genet 2005; 67(3): 230-9. http://dx.doi.org/10.1111/j.1399-0004.2004.00392.x PMID: 15691361

[24] Kennedy L, Bittel DC, Kibiryeva N, Kalra SP, Torto R, Butler MG. Circulating adiponectin levels, body composition and obesity-related variables in Prader–Willi syndrome: Comparison with obese subjects. Int J Obes 2006; 30(2): 382-7. http://dx.doi.org/10.1038/sj.ijo.0803115 PMID: 16231029

[25] Krochik AG, Ozuna B, Torrado M, Chertkoff L, Mazza C. Characterization of alterations in carbohydrate metabolism in children with Prader-Willi syndrome. J Pediatr Endocrinol Metab 2006; 19(7): 911-8. http://dx.doi.org/10.1515/JPEM.2006.19.7.911 PMID: 16995571

[26] Neeland IJ, Turer AT, Ayers CR, *et al.* Dysfunctional adiposity and the risk of prediabetes and type 2 diabetes in obese adults. JAMA 2012; 308(11): 1150-9. http://dx.doi.org/10.1001/2012.jama.11132 PMID: 22990274

[27] Premanath M, Basavanagowdappa H, Mahesh M, Babu MS. Occurrence of diabetes mellitus in obese nondiabetic patients, with correlative analysis of visceral fat, fasting insulin, and insulin resistance: A 3-year follow-up study (mysore visceral adiposity in diabetes follow-up study). Indian J Endocrinol Metab 2017; 21(2): 308-15. http://dx.doi.org/10.4103/ijem.IJEM_418_16 PMID: 28459031

[28] Wu J, Gong L, Li Q, *et al.* A novel visceral adiposity index for prediction of Type 2 diabetes and pre-diabetes in chinese adults: A 5-year prospective study. Sci Rep 2017; 7(1): 13784. http://dx.doi.org/10.1038/s41598-017-14251-w PMID: 29062099

[29] Xia MF, Lin HD, Chen LY, *et al.* Association of visceral adiposity and its longitudinal increase with the risk of diabetes in Chinese adults: A prospective cohort study. Diabetes Metab Res Rev 2018; 34(7): e3048. http://dx.doi.org/10.1002/dmrr.3048 PMID: 30035847

[30] Larsson B, Svärdsudd K, Welin L, Wilhelmsen L, Björntorp P, Tibblin G. Abdominal adipose tissue distribution, obesity, and risk of cardiovascular disease and death: 13 year follow up of participants in the study of men born in 1913. BMJ 1984; 288(6428): 1401-4. http://dx.doi.org/10.1136/bmj.288.6428.1401 PMID: 6426576

[31] Lapidus L, Bengtsson C, Larsson B, Pennert K, Rybo E, Sjöström L. Distribution of adipose tissue and risk of cardiovascular disease and death: A 12 year follow up of participants in the population study of women in Gothenburg, Sweden. BMJ 1984; 289(6454): 1257-61. http://dx.doi.org/10.1136/bmj.289.6454.1257 PMID: 6437507

[32] Ohlson LO, Larsson B, Svärdsudd K, *et al.* The influence of body fat distribution on the incidence of diabetes mellitus. 13.5 years of follow-up of the participants in the study of men born in 1913. Diabetes 1985; 34(10): 1055-8. http://dx.doi.org/10.2337/diab.34.10.1055 PMID: 4043554

[33] Lundgren H, Bengtsson C, Blohme G, Lapidus L, Sjöström L. Adiposity and adipose tissue distribution in relation to incidence of diabetes in women: Results from a prospective population study in Gothenburg, Sweden. Int J Obes 1989; 13(4): 413-23. PMID: 2793297

[34] Olivo RE, Davenport CA, Diamantidis CJ, *et al.* Obesity and synergistic risk factors for chronic kidney disease in African American adults: The Jackson Heart Study. Nephrol Dial Transplant 2018; 33(6): 992-1001. http://dx.doi.org/10.1093/ndt/gfx230 PMID: 28992354

[35] Weyer C, Foley JE, Bogardus C, Tataranni PA, Pratley RE. Enlarged subcutaneous abdominal adipocyte size, but not obesity itself, predicts Type II diabetes independent of insulin resistance. Diabetologia 2000; 43(12): 1498-506. http://dx.doi.org/10.1007/s001250051560 PMID: 11151758

[36] Jansson PA, Pellmé F, Hammarstedt A, *et al.* A novel cellular marker of insulin resistance and early atherosclerosis in humans is related to impaired fat cell differentiation and low adiponectin. FASEB J 2003; 17(11): 1434-40. http://dx.doi.org/10.1096/fj.02-1132com PMID: 12890697

[37] Hammarstedt A, Rotter Sopasakis V, Gogg S, Jansson PA, Smith U. Improved insulin sensitivity and adipose tissue dysregulation after short-term treatment with pioglitazone in non-diabetic, insulin-resistant subjects. Diabetologia 2005; 48(1): 96-104. http://dx.doi.org/10.1007/s00125-004-1612-3 PMID: 15624096

[38] Lundgren M, Svensson M, Lindmark S, Renström F, Ruge T, Eriksson JW. Fat cell enlargement is an independent marker of insulin resistance and 'hyperleptinaemia'. Diabetologia 2007; 50(3): 625-33. http://dx.doi.org/10.1007/s00125-006-0572-1 PMID: 17216279

[39] Alligier M, Gabert L, Meugnier E, *et al.* Visceral fat accumulation during lipid overfeeding is related to subcutaneous adipose tissue characteristics in healthy men. J Clin Endocrinol Metab 2013; 98(2): 802-10. http://dx.doi.org/10.1210/jc.2012-3289 PMID: 23284008

[40] McLaughlin T, Lamendola C, Coghlan N, *et al.* Subcutaneous adipose cell size and distribution: Relationship to insulin resistance and body fat. Obesity (Silver Spring) 2014; 22(3): 673-80. http://dx.doi.org/10.1002/oby.20209 PMID: 23666871

[41] McLaughlin T, Craig C, Liu LF, *et al.* Adipose Cell Size and Regional Fat Deposition as Predictors of Metabolic Response to Overfeeding in Insulin-Resistant and Insulin-Sensitive Humans. Diabetes 2016; 65(5): 1245-54. http://dx.doi.org/10.2337/db15-1213 PMID: 26884438

[42] Lönn M, Mehlig K, Bengtsson C, Lissner L. Adipocyte size predicts incidence of type 2 diabetes in women. FASEB J 2010; 24(1): 326-31. http://dx.doi.org/10.1096/fj.09-133058 PMID: 19741173

[43] Chandalia M, Lin P, Seenivasan T, *et al.* Insulin resistance and body fat distribution in South Asian men compared to Caucasian men. PLoS One 2007; 2(8): e812. http://dx.doi.org/10.1371/journal.pone.0000812 PMID: 17726542

[44] Geberhiwot T, Baig S, Obringer C, *et al.* Relative adipose tissue failure in alström syndrome drives obesity-induced insulin resistance. diabetes 2021; 70(2): 364-76. http://dx.doi.org/10.2337/db20-0647 PMID: 32994277

[45] Vague J. The degree of masculine differentiation of obesities: A factor determining predisposition to diabetes, atherosclerosis, gout, and uric calculous disease. Am J Clin Nutr 1956; 4(1): 20-34. http://dx.doi.org/10.1093/ajcn/4.1.20 PMID: 13282851

[46] Kissebah AH, Vydelingum N, Murray R, *et al.* Relation of body fat distribution to metabolic complications of obesity. J Clin Endocrinol Metab 1982; 54(2): 254-60. http://dx.doi.org/10.1210/jcem-54-2-254 PMID: 7033275

[47] Hartz A, Rupley DC Jr, Kalkhoff RD, Rimm AA. Relationship of obesity to diabetes: Influence of obesity level and body fat distribution. Prev Med 1983; 12(2): 351-7. http://dx.doi.org/10.1016/0091-7435(83)90244-X PMID: 6878197

[48] Krotkiewski M, Björntorp P, Sjöström L, Smith U. Impact of obesity on metabolism in men and women. Importance of regional adipose tissue distribution. J Clin Invest 1983; 72(3): 1150-62. http://dx.doi.org/10.1172/JCI111040 PMID: 6350364

[49] Van Gaal LF, Vansant GA, De Leeuw IH. Upper body adiposity and the risk for atherosclerosis. J Am Coll Nutr 1989; 8(6): 504-14. http://dx.doi.org/10.1080/07315724.1989.10720320 PMID: 2695550

[50] Fujioka S, Matsuzawa Y, Tokunaga K, *et al.* Improvement of glucose and lipid metabolism associated with selective reduction of intra-abdominal visceral fat in premenopausal women with visceral fat obesity. Int J Obes 1991; 15(12): 853-9. PMID: 1794928

[51] Matsuzawa Y, Shimomura I, Nakamura T, Keno Y, Kotani K, Tokunaga K. Pathophysiology and pathogenesis of visceral fat obesity. Obes Res 1995; 3(S2)(Suppl. 2): 187s-94s. http://dx.doi.org/10.1002/j.1550-8528.1995.tb00462.x PMID: 8581775

[52] Yamashita S, Nakamura T, Shimomura L, *et al.* Insulin Resistance and Body Fat Distribution: Contribution of visceral fat accumulation to the development of insulin resistance and atherosclerosis. Diabetes Care 1996; 19(3): 287-91. http://dx.doi.org/10.2337/diacare.19.3.287 PMID: 8742584

[53] Goldstone AP, Thomas EL, Brynes AE, *et al.* Visceral adipose tissue and metabolic complications of obesity are reduced in Prader-Willi syndrome female adults: Evidence for novel influ-

ences on body fat distribution. J Clin Endocrinol Metab 2001; 86(9): 4330-8.
http://dx.doi.org/10.1210/jcem.86.9.7814 PMID: 11549670

[54] Wajchenberg BL, Giannella-Neto D, da Silva ME, Santos RF. Depot-specific hormonal characteristics of subcutaneous and visceral adipose tissue and their relation to the metabolic syndrome. Horm Metab Res 2002; 34(11/12): 616-21.
http://dx.doi.org/10.1055/s-2002-38256 PMID: 12660870

[55] Nicklas BJ, Penninx BWJH, Ryan AS, Berman DM, Lynch NA, Dennis KE. Visceral adipose tissue cutoffs associated with metabolic risk factors for coronary heart disease in women. Diabetes Care 2003; 26(5): 1413-20.
http://dx.doi.org/10.2337/diacare.26.5.1413 PMID: 12716798

[56] Gastaldelli A, Cusi K, Pettiti M, *et al.* Relationship between hepatic/visceral fat and hepatic insulin resistance in nondiabetic and type 2 diabetic subjects. Gastroenterology 2007; 133(2): 496-506.
http://dx.doi.org/10.1053/j.gastro.2007.04.068 PMID: 17681171

[57] Umegaki H, Haimoto H, Ishikawa J, Kario K. Visceral fat contribution of insulin resistance in elderly people. J Am Geriatr Soc 2008; 56(7): 1373-5.
http://dx.doi.org/10.1111/j.1532-5415.2008.01730.x PMID: 18774980

[58] Usui C, Asaka M, Kawano H, *et al.* Visceral fat is a strong predictor of insulin resistance regardless of cardiorespiratory fitness in non-diabetic people. J Nutr Sci Vitaminol (Tokyo) 2010; 56(2): 109-16.
http://dx.doi.org/10.3177/jnsv.56.109 PMID: 20495292

[59] Philipsen A, Jørgensen ME, Vistisen D, *et al.* Associations between ultrasound measures of abdominal fat distribution and indices of glucose metabolism in a population at high risk of type 2 diabetes: The ADDITION-PRO study. PLoS One 2015; 10(4): e0123062.
http://dx.doi.org/10.1371/journal.pone.0123062 PMID: 25849815

[60] Jung SH, Ha KH, Kim DJ. Visceral Fat Mass Has Stronger Associations with Diabetes and Prediabetes than Other Anthropometric Obesity Indicators among Korean Adults. Yonsei Med J 2016; 57(3): 674-80.
http://dx.doi.org/10.3349/ymj.2016.57.3.674 PMID: 26996568

[61] Lee JJ, Pedley A, Hoffmann U, Massaro JM, Levy D, Long MT. Visceral and intrahepatic fat are associated with cardiometabolic risk factors above other ectopic fat depots: The Framingham Heart Study. Am J Med 2018; 131(6): 684-692.e12.
http://dx.doi.org/10.1016/j.amjmed.2018.02.002 PMID: 29518370

[62] Zhang M, Hu T, Zhang S, Zhou L. Associations of different adipose tissue depots with insulin resistance: A Systematic Review and Meta-analysis of Observational Studies. Sci Rep 2015; 5(1): 18495.
http://dx.doi.org/10.1038/srep18495 PMID: 26686961

[63] Gaal LV, Rillaerts E, Creten W, Leeuw ID. Relationship of body fat distribution pattern to atherogenic risk factors in NIDDM. Preliminary results. Diabetes Care 1988; 11(2): 103-6.
http://dx.doi.org/10.2337/diacare.11.2.103 PMID: 3383730

[64] Abate N, Garg A, Peshock RM, Stray-Gundersen J, Adams-Huet B, Grundy SM. Relationship of generalized and regional adiposity to insulin sensitivity in men with NIDDM. Diabetes 1996; 45(12): 1684-93.
http://dx.doi.org/10.2337/diab.45.12.1684 PMID: 8922352

[65] Banerji MA, Buckley MC, Chaiken RL, Gordon D, Lebovitz HE, Kral JG. Liver fat, serum triglycerides and visceral adipose tissue in insulin-sensitive and insulin-resistant black men with NIDDM. Int J Obes Relat Metab Disord 1995; 19(12): 846-50.
PMID: 8963350

[66] Ryysy L, Häkkinen AM, Goto T, *et al.* Hepatic fat content and insulin action on free fatty acids and glucose metabolism rather than insulin absorption are associated with insulin requirements during insulin therapy in type 2 diabetic patients. Diabetes 2000; 49(5): 749-58.
http://dx.doi.org/10.2337/diabetes.49.5.749 PMID: 10905483

[67] Kotronen A, Juurinen L, Tiikkainen M, Vehkavaara S, Yki-Järvinen H. Increased liver fat, impaired insulin clearance, and hepatic and adipose tissue insulin resistance in type 2 diabetes. Gastroenterology 2008; 135(1): 122-30.
http://dx.doi.org/10.1053/j.gastro.2008.03.021 PMID: 18474251

[68] Goto T, Onuma T, Takebe K, Kral JG. The influence of fatty liver on insulin clearance and insulin resistance in non-diabetic Japanese subjects. Int J Obes Relat Metab Disord 1995; 19(12): 841-5.
PMID: 8963349

[69] Sookoian S, Pirola CJ. Systematic review with meta-analysis: Risk factors for non-alcoholic fatty liver disease suggest a shared altered metabolic and cardiovascular profile between lean and obese patients. Aliment Pharmacol Ther 2017; 46(2): 85-95.
http://dx.doi.org/10.1111/apt.14112 PMID: 28464369

[70] Ballestri S, Zona S, Targher G, *et al.* Nonalcoholic fatty liver disease is associated with an almost twofold increased risk of incident type 2 diabetes and metabolic syndrome. Evidence from a systematic review and meta-analysis. J Gastroenterol Hepatol 2016; 31(5): 936-44.
http://dx.doi.org/10.1111/jgh.13264 PMID: 26667191

[71] Alexander M, Loomis AK, van der Lei J, *et al.* Non-alcoholic fatty liver disease and risk of incident acute myocardial infarction and stroke: Findings from matched cohort study of 18 million European adults. BMJ 2019; 367: l5367.
http://dx.doi.org/10.1136/bmj.l5367 PMID: 31594780

[72] Ma W, Wu W, Wen W, *et al.* Association of NAFLD with cardiovascular disease and all-cause mortality: A large-scale prospective cohort study based on UK Biobank. Ther Adv Chronic Dis 2022; 13
http://dx.doi.org/10.1177/20406223221122478 PMID: 36159632

[73] Heni M, Machann J, Staiger H, *et al.* Pancreatic fat is negatively associated with insulin secretion in individuals with impaired fasting glucose and/or impaired glucose tolerance: A nuclear magnetic resonance study. Diabetes Metab Res Rev 2010; 26(3): 200-5.
http://dx.doi.org/10.1002/dmrr.1073 PMID: 20225188

[74] Lu T, Wang Y, Dou T, Xue B, Tan Y, Yang J. Pancreatic fat content is associated with β-cell function and insulin resistance in Chinese type 2 diabetes subjects. Endocr J 2019; 66(3): 265-70.
http://dx.doi.org/10.1507/endocrj.EJ18-0436 PMID: 30700664

[75] Li YX, Sang YQ, Sun Y, *et al.* Pancreatic fat is not significantly correlated with β-cell dysfunction in patients with new-onset Type 2 diabetes mellitus using quantitative computed tomography. Int J Med Sci 2020; 17(12): 1673-82.
http://dx.doi.org/10.7150/ijms.46395 PMID: 32714070

[76] Staaf J, Labmayr V, Paulmichl K, *et al.* Pancreatic fat Is associated with metabolic syndrome and visceral fat but Not beta-cell function or body mass index in pediatric obesity. Pancreas 2017; 46(3): 358-65.
http://dx.doi.org/10.1097/MPA.0000000000000771 PMID: 27941426

[77] Miljkovic I, Kuipers AL, Cvejkus R, *et al.* Myosteatosis increases with aging and is associated with incident diabetes in African ancestry men. Obesity (Silver Spring) 2016; 24(2): 476-82.
http://dx.doi.org/10.1002/oby.21328 PMID: 26694517

[78] Stellingwerff T, Boon H, Jonkers RAM, *et al.* Significant intramyocellular lipid use during prolonged cycling in endurance-trained males as assessed by three different methodologies. Am J Physiol Endocrinol Metab 2007; 292(6): E1715-23.
http://dx.doi.org/10.1152/ajpendo.00678.2006 PMID: 17299080

[79] Smith SR, Lovejoy JC, Greenway F, *et al.* Contributions of total body fat, abdominal subcutaneous adipose tissue compartments, and visceral adipose tissue to the metabolic complications of obesity. Metabolism 2001; 50(4): 425-35.
http://dx.doi.org/10.1053/meta.2001.21693 PMID: 11288037

[80] Kelley DE, Thaete FL, Troost F, Huwe T, Goodpaster BH. Subdivisions of subcutaneous abdominal adipose tissue and insulin resistance. Am J Physiol Endocrinol Metab 2000; 278(5): E941-8.
http://dx.doi.org/10.1152/ajpendo.2000.278.5.E941 PMID: 10780952

[81] Yang M, Lin J, Ma X, *et al.* Truncal and leg fat associations with metabolic risk factors among Chinese adults. Asia Pac J Clin Nutr 2016; 25(4): 798-809.
http://dx.doi.org/10.6133/apjcn.092015.35 PMID: 27702723

[82] Misra A, Vikram NK, Arya S, *et al.* High prevalence of insulin resistance in postpubertal Asian Indian children is associated with adverse truncal body fat patterning, abdominal adiposity and excess body fat. Int J Obes 2004; 28(10): 1217-26.
http://dx.doi.org/10.1038/sj.ijo.0802704 PMID: 15314636

[83] Albu JB, Kovera AJ, Johnson JA. Fat distribution and health in obesity. Ann N Y Acad Sci 2000; 904(1): 491-501. http://dx.doi.org/10.1111/j.1749-6632.2000.tb06505.x PMID: 10865794

[84] Marcus MA, Murphy L, Pi-Sunyer FX, Albu JB. Insulin sensitivity and serum triglyceride level in obese white and black women: Relationship to visceral and truncal subcutaneous fat. Metabolism 1999; 48(2): 194-9. http://dx.doi.org/10.1016/S0026-0495(99)90033-1 PMID: 10024081

[85] Wu C-H, Heshka S, Wang J, *et al.* Truncal fat in relation to total body fat: Influences of age, sex, ethnicity and fatness. Int J Obes 2007; 31(9): 1384-91. http://dx.doi.org/10.1038/sj.ijo.0803624 PMID: 17452992

[86] Numao S, Katayama Y, Nakata Y, Matsuo T, Nakagaichi M, Tanaka K. Association of abdominal fat with metabolic syndrome components in overweight women: Effect of menopausal status. J Physiol Anthropol 2020; 39(1): 12. http://dx.doi.org/10.1186/s40101-020-00222-0 PMID: 32307016

[87] Lambe KG, Tugwood JD. A human peroxisome-proliferator-activated receptor-gamma is activated by inducers of adipogenesis, including thiazolidinedione drugs. Eur J Biochem 1996; 239(1): 1-7. http://dx.doi.org/10.1111/j.1432-1033.1996.0001u.x PMID: 8706692

[88] Fajas L, Auboeuf D, Raspé E, *et al.* The organization, promoter analysis, and expression of the human *PPARgamma* gene. J Biol Chem 1997; 272(30): 18779-89. http://dx.doi.org/10.1074/jbc.272.30.18779 PMID: 9228052

[89] Vidal-Puig AJ, Considine RV, Jimenez-Liñan M, *et al.* Peroxisome proliferator-activated receptor gene expression in human tissues. Effects of obesity, weight loss, and regulation by insulin and glucocorticoids. J Clin Invest 1997; 99(10): 2416-22. http://dx.doi.org/10.1172/JCI119424 PMID: 9153284

[90] Yanase T, Yashiro T, Takitani K, *et al.* Differential expression of PPAR gamma1 and gamma2 isoforms in human adipose tissue. Biochem Biophys Res Commun 1997; 233(2): 320-4. http://dx.doi.org/10.1006/bbrc.1997.6446 PMID: 9144532

[91] Adams M, Montague CT, Prins JB, *et al.* Activators of peroxisome proliferator-activated receptor gamma have depot-specific effects on human preadipocyte differentiation. J Clin Invest 1997; 100(12): 3149-53. http://dx.doi.org/10.1172/JCI119870 PMID: 9399962

[92] Fajas L, Fruchart JC, Auwerx J. PPARγ3 mRNA: A distinct PPARγ mRNA subtype transcribed from an independent promoter. FEBS Lett 1998; 438(1-2): 55-60. http://dx.doi.org/10.1016/S0014-5793(98)01273-3 PMID: 9821958

[93] Auboeuf D, Rieusset J, Fajas L, *et al.* Tissue distribution and quantification of the expression of mRNAs of peroxisome proliferator-activated receptors and liver X receptor-alpha in humans: No alteration in adipose tissue of obese and NIDDM patients. Diabetes 1997; 46(8): 1319-27. http://dx.doi.org/10.2337/diab.46.8.1319 PMID: 9231657

[94] Lefebvre AM, Laville M, Vega N, *et al.* Depot-specific differences in adipose tissue gene expression in lean and obese subjects. Diabetes 1998; 47(1): 98-103. http://dx.doi.org/10.2337/diab.47.1.98 PMID: 9421381

[95] Dubois M, Pattou F, Kerr-Conte J, *et al.* Expression of peroxisome proliferator-activated receptor γ (PPARγ) in normal human pancreatic islet cells. Diabetologia 2000; 43(9): 1165-9. http://dx.doi.org/10.1007/s001250051508 PMID: 11043863

[96] McLaughlin T, Sherman A, Tsao P, *et al.* Enhanced proportion of small adipose cells in insulin-resistant *vs.* insulin-sensitive obese individuals implicates impaired adipogenesis. Diabetologia 2007; 50(8): 1707-15. http://dx.doi.org/10.1007/s00125-007-0708-y PMID: 17549449

[97] Dyment DA, Gibson WT, Huang L, Bassyouni H, Hegele RA, Innes AM. Biallelic mutations at *PPARG* cause a congenital, generalized lipodystrophy similar to the Berardinelli–Seip syndrome. Eur J Med Genet 2014; 57(9): 524-6. http://dx.doi.org/10.1016/j.ejmg.2014.06.006 PMID: 24980513

[98] Francis GA, Li G, Casey R, *et al.* Peroxisomal proliferator activated receptor-γ deficiency in a Canadian kindred with familial partial lipodystrophy type 3 (FPLD3). BMC Med Genet 2006; 7(1): 3. http://dx.doi.org/10.1186/1471-2350-7-3 PMID: 16412238

[99] Rutkowska L, Salachna D, Lewandowski K, Lewiński A, Gach A. Familial partial lipodystrophy-literature review and report of a novel variant in PPARG expanding the spectrum of disease-causing alterations in FPLD3. Diagnostics 2022; 12(5): 1122. http://dx.doi.org/10.3390/diagnostics12051122

[100] Lambadiari V, Kountouri A, Maratou E, Liatis S, Dimitriadis GD, Karpe F. Case report: metreleptin treatment in a patient with a novel mutation for familial partial lipodystrophy Type 3, presenting with uncontrolled diabetes and insulin resistance. front endocrinol (lausanne) 2021; 12: 684182. http://dx.doi.org/10.3389/fendo.2021.684182 PMID: 34168618

[101] Majithia AR, Flannick J, Shahinian P, *et al.* Rare variants in *PPARG* with decreased activity in adipocyte differentiation are associated with increased risk of type 2 diabetes. Proc Natl Acad Sci USA 2014; 111(36): 13127-32. http://dx.doi.org/10.1073/pnas.1410428111 PMID: 25157153

[102] Sarhangi N, Sharifi F, Hashemian L, *et al.* PPARG (Pro12Ala) genetic variant and risk of T2DM: A systematic review and meta-analysis. Sci Rep 2020; 10(1): 12764. http://dx.doi.org/10.1038/s41598-020-69363-7 PMID: 32728045

[103] Kelly IE, Han TS, Walsh K, Lean ME. Effects of a thiazolidinedione compound on body fat and fat distribution of patients with type 2 diabetes. Diabetes Care 1999; 22(2): 288-93. http://dx.doi.org/10.2337/diacare.22.2.288 PMID: 10333947

[104] Mori Y, Murakawa Y, Okada K, *et al.* Effect of troglitazone on body fat distribution in type 2 diabetic patients. Diabetes Care 1999; 22(6): 908-12. http://dx.doi.org/10.2337/diacare.22.6.908 PMID: 10372240

[105] Kawai T, Takei I, Oguma Y, *et al.* Effects of troglitazone on fat distribution in the treatment of male type 2 diabetes. Metabolism 1999; 48(9): 1102-7. http://dx.doi.org/10.1016/S0026-0495(99)90122-1 PMID: 10484048

[106] Arioglu E, Duncan-Morin J, Sebring N, *et al.* Efficacy and safety of troglitazone in the treatment of lipodystrophy syndromes. Ann Intern Med 2000; 133(4): 263-74. http://dx.doi.org/10.7326/0003-4819-133-4-200008150-00009 PMID: 10929166

[107] Katoh S, Hata S, Matsushima M, *et al.* Troglitazone prevents the rise in visceral adiposity and improves fatty liver associated with sulfonylurea therapy—A randomized controlled trial. Metabolism 2001; 50(4): 414-7. http://dx.doi.org/10.1053/meta.2001.21691 PMID: 11288035

[108] Ciaraldi TP, Kong APS, Chu NV, *et al.* Regulation of glucose transport and insulin signaling by troglitazone or metformin in adipose tissue of type 2 diabetic subjects. Diabetes 2002; 51(1): 30-6. http://dx.doi.org/10.2337/diabetes.51.1.30 PMID: 11756319

[109] Miyazaki Y, Mahankali A, Matsuda M, *et al.* Effect of pioglitazone on abdominal fat distribution and insulin sensitivity in type 2 diabetic patients. J Clin Endocrinol Metab 2002; 87(6): 2784-91. http://dx.doi.org/10.1210/jcem.87.6.8567 PMID: 12050251

[110] Bajaj M, Suraamornkul S, Pratipanawatr T, *et al.* Pioglitazone reduces hepatic fat content and augments splanchnic glucose uptake in patients with type 2 diabetes. Diabetes 2003; 52(6): 1364-70. http://dx.doi.org/10.2337/diabetes.52.6.1364 PMID: 12765945

[111] Schernthaner G, Matthews DR, Charbonnel B, Hanefeld M, Brunetti P. Efficacy and safety of pioglitazone *versus* metformin in patients with type 2 diabetes mellitus: A double-blind, randomized trial. J Clin Endocrinol Metab 2004; 89(12): 6068-76. http://dx.doi.org/10.1210/jc.2003-030861 PMID: 15579760

[112] Smith SR, de Jonge L, Volaufova J, Li Y, Xie H, Bray GA. Effect of pioglitazone on body composition and energy expenditure: A randomized controlled trial. Metabolism 2005; 54(1): 24-32. http://dx.doi.org/10.1016/j.metabol.2004.07.008 PMID: 15562376

[113] Kodama N, Tahara N, Tahara A, *et al.* Effects of pioglitazone on visceral fat metabolic activity in impaired glucose tolerance or type 2 diabetes mellitus. J Clin Endocrinol Metab 2013; 98(11): 4438-45.

http://dx.doi.org/10.1210/jc.2013-2920 PMID: 24030946

[114] Filipova E, Uzunova K, Kalinov K, Vekov T. Effects of pioglitazone therapy on blood parameters, weight and BMI: A meta-analysis. Diabetol Metab Syndr 2017; 9(1): 90. http://dx.doi.org/10.1186/s13098-017-0290-5 PMID: 29163673

[115] Nakamura T, Funahashi T, Yamashita S, *et al.* Thiazolidinedione derivative improves fat distribution and multiple risk factors in subjects with visceral fat accumulation—double-blind placebo-controlled trial. Diabetes Res Clin Pract 2001; 54(3): 181-90. http://dx.doi.org/10.1016/S0168-8227(01)00319-9 PMID: 11689273

[116] Bray GA, Smith SR, Banerji MA, *et al.* Effect of pioglitazone on body composition and bone density in subjects with prediabetes in the ACT NOW trial. Diabetes Obes Metab 2013; 15(10): 931-7. http://dx.doi.org/10.1111/dom.12099 PMID: 23551856

[117] Nolan JJ, Ludvik B, Beerdsen P, Joyce M, Olefsky J. Improvement in glucose tolerance and insulin resistance in obese subjects treated with troglitazone. N Engl J Med 1994; 331(18): 1188-93. http://dx.doi.org/10.1056/NEJM199411033311803 PMID: 7935656

[118] Suter SL, Nolan JJ, Wallace P, Gumbiner B, Olefsky JM. Metabolic effects of new oral hypoglycemic agent CS-045 in NIDDM subjects. Diabetes Care 1992; 15(2): 193-203. http://dx.doi.org/10.2337/diacare.15.2.193 PMID: 1547676

[119] Inzucchi SE, Maggs DG, Spollett GR, *et al.* Efficacy and metabolic effects of metformin and troglitazone in type II diabetes mellitus. N Engl J Med 1998; 338(13): 867-73. http://dx.doi.org/10.1056/NEJM199803263381303 PMID: 9516221

[120] Maggs DG, Buchanan TA, Burant CF, *et al.* Metabolic effects of troglitazone monotherapy in type 2 diabetes mellitus. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 1998; 128(3): 176-85. http://dx.doi.org/10.7326/0003-4819-128-3-199802010-00002 PMID: 9454525

[121] Koivisto VA, Pelkonen R, Cantell K. Effect of interferon on glucose tolerance and insulin sensitivity. Diabetes 1989; 38(5): 641-7. http://dx.doi.org/10.2337/diab.38.5.641 PMID: 2653935

[122] Shiba T, Higashi N, Nishimura Y. Hyperglycaemia due to insulin resistance caused by interferon-γ. Diabet Med 1998; 15(5): 435-6. http://dx.doi.org/10.1002/(SICI)1096-9136(199805)15:5<435::AID-DIA566>3.0.CO;2-N PMID: 9609368

[123] Ghosh AR, Bhattacharya R, Bhattacharya S, *et al.* Adipose recruitment and activation of plasmacytoid dendritic cells fuel metaflammation. Diabetes 2016; 65(11): 3440-52. http://dx.doi.org/10.2337/db16-0331 PMID: 27561727

[124] Faber DR, van der Graaf Y, Westerink J, Kanhai DA, Monajemi H, Visseren FLJ. Hepatocyte growth factor and interferon-γ inducible protein-10 are related to visceral adiposity. Eur J Clin Invest 2013; 43(4): 369-78. http://dx.doi.org/10.1111/eci.12054 PMID: 23398210

[125] O'Rourke RW, Metcalf MD, White AE, *et al.* Depot-specific differences in inflammatory mediators and a role for NK cells and IFN-γ in inflammation in human adipose tissue. Int J Obes 2009; 33(9): 978-90. http://dx.doi.org/10.1038/ijo.2009.133 PMID: 19564875

[126] Bradley D, Smith AJ, Blaszczak A, *et al.* Interferon gamma mediates the reduction of adipose tissue regulatory T cells in human obesity. Nat Commun 2022; 13(1): 5606. http://dx.doi.org/10.1038/s41467-022-33067-5 PMID: 36153324

[127] McGillicuddy FC, Chiquoine EH, Hinkle CC, *et al.* Interferon gamma attenuates insulin signaling, lipid storage, and differentiation in human adipocytes *via* activation of the JAK/STAT pathway. J Biol Chem 2009; 284(46): 31936-44. http://dx.doi.org/10.1074/jbc.M109.061655 PMID: 19776010

[128] Wentworth JM, Zhang J-G, Bandala-Sanchez E, *et al.* Interferon-gamma released from omental adipose tissue of insulin-resistant humans alters adipocyte phenotype and impairs response to insulin and adiponectin release. Int J Obes 2017; 41(12): 1782-9. http://dx.doi.org/10.1038/ijo.2017.180 PMID: 28769120

[129] Vandorpe DH, Heneghan JF, Waitzman JS, *et al.* Apolipoprotein L1 (APOL1) cation current in HEK-293 cells and in human podocytes. Pflugers Arch 2023; 475(3): 323-41. http://dx.doi.org/10.1007/s00424-022-02767-8 PMID: 36449077

[130] Davis SE, Khatua AK, Popik W. Nucleosomal dsDNA stimulates APOL1 expression in human cultured podocytes by activating the cGAS/IFI16-STING signaling pathway. Sci Rep 2019; 9(1): 15485. http://dx.doi.org/10.1038/s41598-019-51998-w PMID: 31664093

[131] Kumar V, Vashistha H, Lan X, *et al.* Role of Apolipoprotein L1 in Human Parietal Epithelial Cell Transition. Am J Pathol 2018; 188(11): 2508-28. http://dx.doi.org/10.1016/j.ajpath.2018.07.025 PMID: 30201495

[132] Nichols B, Jog P, Lee JH, *et al.* Innate immunity pathways regulate the nephropathy gene Apolipoprotein L1. Kidney Int 2015; 87(2): 332-42. http://dx.doi.org/10.1038/ki.2014.270 PMID: 25100047

[133] Taylor HE, Khatua AK, Popik W. The innate immune factor apolipoprotein L1 restricts HIV-1 infection. J Virol 2014; 88(1): 592-603. http://dx.doi.org/10.1128/JVI.02828-13 PMID: 24173214

[134] Zhaorigetu S, Wan G, Kaini R, Wan G, Jiang Z, Hu CA. ApoL1, a BH3-only lipid-binding protein, induces autophagic cell death. Autophagy 2008; 4(8): 1079-82. http://dx.doi.org/10.4161/auto.7066 PMID: 18927493

[135] Genovese G, Friedman DJ, Ross MD, *et al.* Association of trypanolytic ApoL1 variants with kidney disease in African Americans. Science 2010; 329(5993): 841-5. http://dx.doi.org/10.1126/science.1193032 PMID: 20647424

[136] Tzur S, Rosset S, Shemer R, *et al.* Missense mutations in the APOL1 gene are highly associated with end stage kidney disease risk previously attributed to the MYH9 gene. Hum Genet 2010; 128(3): 345-50. http://dx.doi.org/10.1007/s00439-010-0861-0 PMID: 20635188

[137] Chun J, Zhang JY, Wilkins MS, *et al.* Recruitment of APOL1 kidney disease risk variants to lipid droplets attenuates cell toxicity. Proc Natl Acad Sci USA 2019; 116(9): 3712-21. http://dx.doi.org/10.1073/pnas.1820414116 PMID: 30733285

[138] Chun J, Riella CV, Chung H, *et al.* DGAT2 inhibition potentiates lipid droplet formation to reduce cytotoxicity in APOL1 kidney risk variants. J Am Soc Nephrol 2022; 33(5): 889-907. http://dx.doi.org/10.1681/ASN.2021050723 PMID: 35232775

[139] Nadkarni GN, Galarneau G, Ellis SB, *et al.* Apolipoprotein L1 variants and blood pressure traits in african americans. J Am Coll Cardiol 2017; 69(12): 1564-74. http://dx.doi.org/10.1016/j.jacc.2017.01.040 PMID: 28335839

[140] Nadkarni GN, Fei K, Galarneau G, *et al.* APOL1 renal risk variants are associated with obesity and body composition in African ancestry adults. Medicine (Baltimore) 2021; 100(45): e27785. http://dx.doi.org/10.1097/MD.0000000000027785 PMID: 34766590

[141] Friedman DJ, Kozlitina J, Genovese G, Jog P, Pollak MR. Population-based risk assessment of APOL1 on renal disease. J Am Soc Nephrol 2011; 22(11): 2098-105. http://dx.doi.org/10.1681/ASN.2011050519 PMID: 21997396

[142] Parsa A, Kao WHL, Xie D, *et al.* APOL1 risk variants, race, and progression of chronic kidney disease. N Engl J Med 2013; 369(23): 2183-96. http://dx.doi.org/10.1056/NEJMoa1310345 PMID: 24206458

[143] Freedman BI, Rocco MV, Bates JT, *et al. APOL1* renal-risk variants do not associate with incident cardiovascular disease or mortality in the Systolic Blood Pressure Intervention Trial. Kidney Int Rep 2017; 2(4): 713-20. http://dx.doi.org/10.1016/j.ekir.2017.03.008 PMID: 28758155

[144] Chen TK, Katz R, Estrella MM, *et al.* Association Between *APOL1* Genotypes and Risk of Cardiovascular Disease in MESA (Multi-Ethnic Study of Atherosclerosis). J Am Heart Assoc 2017; 6(12): e007199. http://dx.doi.org/10.1161/JAHA.117.007199 PMID: 29269352

[145] Bick AG, Akwo E, Robinson-Cohen C, *et al.* Association of *APOL1* risk alleles with cardiovascular disease in blacks in the million veteran program. Circulation 2019; 140(12): 1031-40. http://dx.doi.org/10.1161/CIRCULATIONAHA.118.036589 PMID: 31337231

[146] Hoy WE, Hughson MD, Kopp JB, Mott SA, Bertram JF, Winkler CA. APOL1 Risk Alleles Are Associated with Exaggerated Age-Related Changes in Glomerular Number and Volume in African-American Adults. J Am Soc Nephrol 2015; 26(12): 3179-89.

http://dx.doi.org/10.1681/ASN.2014080768 PMID: 26038529
[147] Hughson MD, Hoy WE, Mott SA, *et al. APOL1* risk alleles are associated with more severe arteriosclerosis in renal resistance vessels with aging and hypertension. Kidney Int Rep 2016; 1(1): 10-23.
http://dx.doi.org/10.1016/j.ekir.2016.03.002 PMID: 27610422
[148] Valdez Imbert R, Hti Lar Seng NS, Stokes MB, Jim B. Obesity-related glomerulopathy in the presence of APOL1 risk alleles. BMJ Case Rep 2022; 15(8): e249624.
http://dx.doi.org/10.1136/bcr-2022-249624 PMID: 35985743
[149] Eiholzer U, Blum WF, Molinari L. Body fat determined by skinfold measurements is elevated despite underweight in infants with Prader-Labhart-Willi syndrome. J Pediatr 1999; 134(2): 222-5.
http://dx.doi.org/10.1016/S0022-3476(99)70419-1 PMID: 9931533
[150] Bekx MT, Carrel AL, Shriver TC, Li Z, Allen DB. Decreased energy expenditure is caused by abnormal body composition in infants with Prader-Willi Syndrome. J Pediatr 2003; 143(3): 372-6.
http://dx.doi.org/10.1067/S0022-3476(03)00386-X PMID: 14517523
[151] Olarescu NC, Jørgensen AP, Godang K, Jurik AG, Frøslie KF, Bollerslev J. Dual-energy X-ray absorptiometry is a valid method to estimate visceral adipose tissue in adult patients with Prader-Willi syndrome during treatment with growth hormone. J Clin Endocrinol Metab 2014; 99(9): E1727-31.
http://dx.doi.org/10.1210/jc.2014-2059 PMID: 24955611
[152] van Nieuwpoort IC, Twisk JWR, Curfs LMG, Lips P, Drent ML. Body composition, adipokines, bone mineral density and bone remodeling markers in relation to IGF-1 levels in adults with Prader-Willi syndrome. Int J Pediatr Endocrinol 2018; 2018(1): 1.
http://dx.doi.org/10.1186/s13633-018-0055-4 PMID: 29371863
[153] Mai S, Fintini D, Mele C, *et al.* Circulating irisin in children and Adolescents With Prader-willi syndrome: relation with glucose metabolism. front endocrinol (lausanne) 2022; 13: 918467.
http://dx.doi.org/10.3389/fendo.2022.918467 PMID: 35774143
[154] Brambilla P, Bosio L, Manzoni P, Pietrobelli A, Beccaria L, Chiumello G. Peculiar body composition in patients with Prader-Labhart-Willi syndrome. Am J Clin Nutr 1997; 65(5): 1369-74.
http://dx.doi.org/10.1093/ajcn/65.5.1369 PMID: 9129464
[155] Theodoro MF, Talebizadeh Z, Butler MG. Body composition and fatness patterns in Prader-Willi syndrome: Comparison with simple obesity. Obesity (Silver Spring) 2006; 14(10): 1685-90.
http://dx.doi.org/10.1038/oby.2006.193 PMID: 17062796
[156] Sode-Carlsen R, Farholt S, Rabben KF, *et al.* Body composition, endocrine and metabolic profiles in adults with Prader-Willi syndrome. Growth Horm IGF Res 2010; 20(3): 179-84.
http://dx.doi.org/10.1016/j.ghir.2009.12.004 PMID: 20199883
[157] Tanaka Y, Abe Y, Oto Y, *et al.* Characterization of fat distribution in Prader-Willi syndrome: Relationships with adipocytokines and influence of growth hormone treatment. Am J Med Genet A 2013; 161(1): 27-33.
http://dx.doi.org/10.1002/ajmg.a.35653 PMID: 23239671
[158] l'Allemand D, Eiholzer U, Schlumpf M, Torresani T, Girard J. Carbohydrate metabolism is not impaired after 3 years of growth hormone therapy in children with Prader-Willi syndrome. Horm Res Paediatr 2003; 59(5): 239-48.
http://dx.doi.org/10.1159/000070224 PMID: 12714788
[159] Rosenberg AGW, Passone CGB, Pellikaan K, *et al.* Growth hormone treatment for adults with prader-willi syndrome: a meta-analysis. J Clin Endocrinol Metab 2021; 106(10): 3068-91.
http://dx.doi.org/10.1210/clinem/dgab406 PMID: 34105729
[160] Haqq AM, Muehlbauer MJ, Newgard CB, Grambow S, Freemark M. The metabolic phenotype of Prader-Willi syndrome (PWS) in childhood: Heightened insulin sensitivity relative to body mass index. J Clin Endocrinol Metab 2011; 96(1): E225-32.
http://dx.doi.org/10.1210/jc.2010-1733 PMID: 20962018
[161] Cadoudal T, Buléon M, Sengenès C, *et al.* Impairment of adipose tissue in Prader–Willi syndrome rescued by growth hormone treatment. Int J Obes 2014; 38(9): 1234-40.
http://dx.doi.org/10.1038/ijo.2014.3 PMID: 24406482
[162] Lacroix D, Moutel S, Coupaye M, *et al.* Metabolic and adipose tissue signatures in adults with Prader-Willi syndrome: A model of extreme adiposity. J Clin Endocrinol Metab 2015; 100(3): 850-9.
http://dx.doi.org/10.1210/jc.2014-3127 PMID: 25478934
[163] Fintini D, Grugni G, Bocchini S, *et al.* Disorders of glucose metabolism in Prader–Willi syndrome: Results of a multicenter Italian cohort study. Nutr Metab Cardiovasc Dis 2016; 26(9): 842-7.
http://dx.doi.org/10.1016/j.numecd.2016.05.010 PMID: 27381990
[164] Yang A, Kim J, Cho SY, Jin DK. Prevalence and risk factors for type 2 diabetes mellitus with Prader–Willi syndrome: A single center experience. Orphanet J Rare Dis 2017; 12(1): 146.
http://dx.doi.org/10.1186/s13023-017-0702-5 PMID: 28854950
[165] Schuster DP, Osei K, Zipf WB. Characterization of alterations in glucose and insulin metabolism in Prader-Willi subjects. Metabolism 1996; 45(12): 1514-20.
http://dx.doi.org/10.1016/S0026-0495(96)90181-X PMID: 8969285
[166] Eiholzer U, Stutz K, Weinmann C, Torresani T, Molinari L, Prader A. Low insulin, IGF-I and IGFBP-3 levels in children with Prader-Labhart-Willi syndrome. Eur J Pediatr 1998; 157(11): 890-3.
http://dx.doi.org/10.1007/s004310050961 PMID: 9835431
[167] Oliveira CRP, Salvatori R, Barreto-Filho JAS, *et al.* Insulin sensitivity and β-cell function in adults with lifetime, untreated isolated growth hormone deficiency. J Clin Endocrinol Metab 2012; 97(3): 1013-9.
http://dx.doi.org/10.1210/jc.2011-2590 PMID: 22170707
[168] Vicente TAR, Rocha ÍES, Salvatori R, *et al.* Lifetime congenital isolated GH deficiency does not protect from the development of diabetes. Endocr Connect 2013; 2(2): 112-7.
http://dx.doi.org/10.1530/EC-13-0014 PMID: 23795286
[169] Hedgeman E, Ulrichsen SP, Carter S, *et al.* Long-term health outcomes in patients with Prader–Willi Syndrome: A nationwide cohort study in Denmark. Int J Obes 2017; 41(10): 1531-8.
http://dx.doi.org/10.1038/ijo.2017.139 PMID: 28634363
[170] Manzardo AM, Loker J, Heinemann J, Loker C, Butler MG. Survival trends from the Prader–Willi Syndrome Association (USA) 40-year mortality survey. Genet Med 2018; 20(1): 24-30.
http://dx.doi.org/10.1038/gim.2017.92 PMID: 28682308
[171] Pacoricona Alfaro DL, Lemoine P, Ehlinger V, *et al.* Causes of death in Prader-Willi syndrome: Lessons from 11 years' experience of a national reference center. Orphanet J Rare Dis 2019; 14(1): 238.
http://dx.doi.org/10.1186/s13023-019-1214-2 PMID: 31684997
[172] Oral EA, Simha V, Ruiz E, *et al.* Leptin-replacement therapy for lipodystrophy. N Engl J Med 2002; 346(8): 570-8.
http://dx.doi.org/10.1056/NEJMoa012437 PMID: 11856796
[173] Beltrand J, Beregszaszi M, Chevenne D, *et al.* Metabolic correction induced by leptin replacement treatment in young children with Berardinelli-Seip congenital lipoatrophy. Pediatrics 2007; 120(2): e291-6.
http://dx.doi.org/10.1542/peds.2006-3165 PMID: 17671040
[174] Chan JL, Lutz K, Cochran E, *et al.* Clinical effects of long-term metreleptin treatment in patients with lipodystrophy. Endocr Pract 2011; 17(6): 922-32.
http://dx.doi.org/10.4158/EP11229.OR PMID: 22068254
[175] Diker-Cohen T, Cochran E, Gorden P, Brown RJ. Partial and generalized lipodystrophy: Comparison of baseline characteristics and response to metreleptin. J Clin Endocrinol Metab 2015; 100(5): 1802-10.
http://dx.doi.org/10.1210/jc.2014-4491 PMID: 25734254
[176] Brown RJ, Meehan CA, Cochran E, *et al.* Effects of metreleptin in pediatric patients with lipodystrophy. J Clin Endocrinol Metab 2017; 102(5): 1511-9.
http://dx.doi.org/10.1210/jc.2016-3628 PMID: 28324110
[177] Sekizkardes H, Cochran E, Malandrino N, Garg A, Brown RJ. Efficacy of metreleptin treatment in familial partial lipodystrophy due to *PPARG vs.* LMNA pathogenic variants. J Clin Endocrinol Metab 2019; 104(8): 3068-76.
http://dx.doi.org/10.1210/jc.2018-02787 PMID: 31194872
[178] Nguyen ML, Sachdev V, Burklow TR, *et al.* Leptin attenuates cardiac hypertrophy in patients with generalized lipodystrophy. J Clin Endocrinol Metab 2021; 106(11): e4327-39.
http://dx.doi.org/10.1210/clinem/dgab499 PMID: 34223895
[179] Mosbah H, Vantyghem MC, Nobécourt E, *et al.* Therapeutic indications and metabolic effects of metreleptin in patients with lipodystrophy syndromes: Real-life experience from a national reference network. Diabetes Obes Metab 2022; 24(8): 1565-77.
http://dx.doi.org/10.1111/dom.14726 PMID: 35445532

[180] Lima JG, Nobrega LHC, Lima NN, *et al.* Causes of death in patients with Berardinelli-Seip congenital generalized lipodystrophy. PLoS One 2018; 13(6): e0199052. http://dx.doi.org/10.1371/journal.pone.0199052 PMID: 29883474

[181] Montenegro Junior RM, Lima GECP, Fernandes VO, *et al.* Leu124Serfs*26, a novel *AGPAT2* mutation in congenital generalized lipodystrophy with early cardiovascular complications. Diabetol Metab Syndr 2020; 12(1): 28. http://dx.doi.org/10.1186/s13098-020-00538-y PMID: 32280377

[182] Simha V, Garg A. Phenotypic heterogeneity in body fat distribution in patients with congenital generalized lipodystrophy caused by mutations in the AGPAT2 or seipin genes. J Clin Endocrinol Metab 2003; 88(11): 5433-7. http://dx.doi.org/10.1210/jc.2003-030835 PMID: 14602785

[183] Agarwal AK, Simha V, Oral EA, *et al.* Phenotypic and genetic heterogeneity in congenital generalized lipodystrophy. J Clin Endocrinol Metab 2003; 88(10): 4840-7. http://dx.doi.org/10.1210/jc.2003-030855 PMID: 14557463

[184] Yamamoto A, Kusakabe T, Sato K, Tokizaki T, Sakurai K, Abe S. Seipin-linked congenital generalized lipodystrophy type 2: A rare case with multiple lytic and pseudo-osteopoikilosis lesions. Acta Radiol Open 2019; 8(12): 2058460119892407.

[185] Kim CA, Delépine M, Boutet E, *et al.* Association of a homozygous nonsense caveolin-1 mutation with Berardinelli-Seip congenital lipodystrophy. J Clin Endocrinol Metab 2008; 93(4): 1129-34. http://dx.doi.org/10.1210/jc.2007-1328 PMID: 18211975

[186] Schrauwen I, Szelinger S, Siniard AL, *et al.* A Frame-Shift Mutation in CAV1 Is Associated with a Severe Neonatal Progeroid and Lipodystrophy Syndrome. PLoS One 2015; 10(7): e0131797. http://dx.doi.org/10.1371/journal.pone.0131797 PMID: 26176221

[187] Karhan AN, Zammouri J, Auclair M, *et al.* Biallelic CAV1 null variants induce congenital generalized lipodystrophy with achalasia. Eur J Endocrinol 2021; 185(6): 841-54. http://dx.doi.org/10.1530/EJE-21-0915 PMID: 34643546

[188] Cao H, Alston L, Ruschman J, Hegele RA. Heterozygous CAV1 frameshift mutations (MIM 601047) in patients with atypical partial lipodystrophy and hypertriglyceridemia. Lipids Health Dis 2008; 7(1): 3. http://dx.doi.org/10.1186/1476-511X-7-3 PMID: 18237401

[189] Hayashi YK, Matsuda C, Ogawa M, *et al.* Human PTRF mutations cause secondary deficiency of caveolins resulting in muscular dystrophy with generalized lipodystrophy. J Clin Invest 2009; 119(9): 2623-33. http://dx.doi.org/10.1172/JCI38660 PMID: 19726876

[190] Rajab A, Straub V, McCann LJ, *et al.* Fatal cardiac arrhythmia and long-QT syndrome in a new form of congenital generalized lipodystrophy with muscle rippling (CGL4) due to PTRF-CAVIN mutations. PLoS Genet 2010; 6(3): e1000874. http://dx.doi.org/10.1371/journal.pgen.1000874 PMID: 20300641

[191] Nilay Güneş , Kutlu T, Tekant GT, *et al.* Congenital generalized lipodystrophy: The evaluation of clinical follow-up findings in a series of five patients with type 1 and two patients with type 4. Eur J Med Genet 2020; 63(4): 103819. http://dx.doi.org/10.1016/j.ejmg.2019.103819 PMID: 31778856

[192] Adiyaman SC. Congenital generalized lipodystrophy type 4 due to a novel PTRF/CAVIN1 pathogenic variant in a child: Effects of metreleptin substitution. J Pediatr Endocrinol Metab 2022; 35(7): 946-52.

[193] Patni N, Vuitch F, Garg A. Postmortem Findings in a Young Man With Congenital Generalized Lipodystrophy, Type 4 Due to CAVIN1 Mutations. J Clin Endocrinol Metab 2019; 104(3): 957-60. http://dx.doi.org/10.1210/jc.2018-01331 PMID: 30476128

[194] Knebel B, Kotzka J, Lehr S, *et al.* A mutation in the c-Fos gene associated with congenital generalized lipodystrophy. Orphanet J Rare Dis 2013; 8(1): 119. http://dx.doi.org/10.1186/1750-1172-8-119 PMID: 23919306

[195] Treiber G, Flaus Furmaniuk A, Guilleux A, *et al.* A recurrent familial partial lipodystrophy due to a monoallelic or biallelic LMNA founder variant highlights the multifaceted cardiac manifestations of metabolic laminopathies. Eur J Endocrinol 2021; 185(4): 453-62. http://dx.doi.org/10.1530/EJE-21-0282 PMID: 34292171

[196] Kadowaki T, Kadowaki H, Rechler MM, *et al.* Five mutant alleles of the insulin receptor gene in patients with genetic forms of insulin resistance. J Clin Invest 1990; 86(1): 254-64. http://dx.doi.org/10.1172/JCI114693 PMID: 2365819

[197] Musso C, Cochran E, Moran SA, *et al.* Clinical course of genetic diseases of the insulin receptor (type A and Rabson-Mendenhall syndromes): A 30-year prospective. Medicine (Baltimore) 2004; 83(4): 209-22. http://dx.doi.org/10.1097/01.md.0000133625.73570.54 PMID: 15232309

[198] Semple RK, Sleigh A, Murgatroyd PR, *et al.* Postreceptor insulin resistance contributes to human dyslipidemia and hepatic steatosis. J Clin Invest 2009; 119(2): 315-22. http://dx.doi.org/10.1172/JCI37432 PMID: 19164855

[199] Iwanishi M, Kusakabe T, Azuma C, *et al.* Clinical characteristics in two patients with partial lipodystrophy and Type A insulin resistance syndrome due to a novel heterozygous missense mutation in the insulin receptor gene. Diabetes Res Clin Pract 2019; 152: 79-87. http://dx.doi.org/10.1016/j.diabres.2019.04.034 PMID: 31102683

[200] Al-Hussaini AA, Sulaiman NM, AlZahrani MD, Alenizi AS, Khan M. Prevalence of hepatopathy in type 1 diabetic children. BMC Pediatr 2012; 12(1): 160. http://dx.doi.org/10.1186/1471-2431-12-160 PMID: 23039762

[201] El-Karaksy HM, Anwar G, Esmat G, *et al.* Prevalence of hepatic abnormalities in a cohort of Egyptian children with type 1 diabetes mellitus. Pediatr Diabetes 2010; 11(7): 462-70. http://dx.doi.org/10.1111/j.1399-5448.2009.00627.x PMID: 20042012

[202] Ogilvy-Stuart AL, Soos MA, Hands SJ, Anthony MY, Dunger DB, O'Rahilly S. Hypoglycemia and resistance to ketoacidosis in a subject without functional insulin receptors. J Clin Endocrinol Metab 2001; 86(7): 3319-26. http://dx.doi.org/10.1210/jcem.86.7.7631 PMID: 11443207

[203] Brown RJ, Cochran E, Gorden P. Metreleptin improves blood glucose in patients with insulin receptor mutations. J Clin Endocrinol Metab 2013; 98(11): E1749-56. http://dx.doi.org/10.1210/jc.2013-2317 PMID: 23969187

[204] Tuhan H, Ceylaner S, Nalbantoğlu Ö, *et al.* A Mutation in INSR in a child presenting with severe acanthosis nigricans. J Clin Res Pediatr Endocrinol 2017; 9(4): 371-4. http://dx.doi.org/10.4274/jcrpe.4577 PMID: 28663160

[205] Güemes M, Rahman SA, Shah P, Hussain K. Enteroinsular hormones in two siblings with donohue syndrome and complete leptin deficiency. Pediatr Diabetes 2018; 19(4): 675-9. http://dx.doi.org/10.1111/pedi.12619 PMID: 29226618

[206] Rojek A, Wikiera B, Noczynska A, Niedziela M. Syndrome of congenital insulin resistance caused by a novel *INSR* gene mutation. J Clin Res Pediatr Endocrinol 2021; 0(0): 0. http://dx.doi.org/10.4274/jcrpe.galenos.2021.2021.0256 PMID: 34965699

[207] Longo N, Singh R, Griffin LD, Langley SD, Parks JS, Elsas LJ. Impaired growth in Rabson-Mendenhall syndrome: Lack of effect of growth hormone and insulin-like growth factor-I. J Clin Endocrinol Metab 1994; 79(3): 799-805. http://dx.doi.org/10.1210/jcem.79.3.8077364 PMID: 8077364

[208] Kirel B, Bozdağ O, Köşger P, Aydoğdu SD, Alincak E, Tekin N. A case of Donohue syndrome "Leprechaunism" with a novel mutation in the insulin receptor gene. Turk Pediatri Ars 2018; 52(4): 226-30. http://dx.doi.org/10.5152/TurkPediatriArs.2017.3193 PMID: 29483803

[209] Takasawa K, Tsuji-Hosokawa A, Takishima S, *et al.* Clinical characteristics of adolescent cases with Type A insulin resistance syndrome caused by heterozygous mutations in the β-subunit of the insulin receptor (*INSR*) gene. J Diabetes 2019; 11(1): 46-54. http://dx.doi.org/10.1111/1753-0407.12797 PMID: 29877041

[210] Verdecchia F, Akcan N, Dastamani A, Morgan K, Semple RK, Shah P. Unusual glycemic presentations in a child with a novel heterozygous intragenic INSR deletion. Horm Res Paediatr 2020; 93(6): 396-401. http://dx.doi.org/10.1159/000510462 PMID: 33040071

[211] Kapeller R, Chakrabarti R, Cantley L, Fay F, Corvera S. Internalization of activated platelet-derived growth factor receptor-

phosphatidylinositol-3′ kinase complexes: Potential interactions with the microtubule cytoskeleton. Mol Cell Biol 1993; 13(10): 6052-63.
http://dx.doi.org/10.1128/mcb.13.10.6052-6063.1993 PMID: 8413207

[212] Schwingshandl J, Mache CJ, Rath K, Borkenstein MH. SHORT syndrome and insulin resistance. Am J Med Genet 1993; 47(6): 907-9.
http://dx.doi.org/10.1002/ajmg.1320470619 PMID: 8279490

[213] Dyment DA, Smith AC, Alcantara D, *et al.* Mutations in PIK3R1 cause SHORT syndrome. Am J Hum Genet 2013; 93(1): 158-66.
http://dx.doi.org/10.1016/j.ajhg.2013.06.005 PMID: 23810382

[214] Chudasama KK, Winnay J, Johansson S, *et al.* SHORT syndrome with partial lipodystrophy due to impaired phosphatidylinositol 3 kinase signaling. Am J Hum Genet 2013; 93(1): 150-7.
http://dx.doi.org/10.1016/j.ajhg.2013.05.023 PMID: 23810379

[215] Thauvin-Robinet C, Auclair M, Duplomb L, *et al.* PIK3R1 mutations cause syndromic insulin resistance with lipoatrophy. Am J Hum Genet 2013; 93(1): 141-9.
http://dx.doi.org/10.1016/j.ajhg.2013.05.019 PMID: 23810378

[216] Schroeder C, Riess A, Bonin M, *et al. PIK3R1* mutations in SHORT syndrome. Clin Genet 2014; 86(3): 292-4.
http://dx.doi.org/10.1111/cge.12263 PMID: 23980586

[217] George S, Rochford JJ, Wolfrum C, *et al.* A family with severe insulin resistance and diabetes due to a mutation in AKT2. Science 2004; 304(5675): 1325-8.
http://dx.doi.org/10.1126/science.1096706 PMID: 15166380

[218] Tan K, Kimber WA, Luan J, *et al.* Analysis of genetic variation in Akt2/PKB-beta in severe insulin resistance, lipodystrophy, type 2 diabetes, and related metabolic phenotypes. Diabetes 2007; 56(3): 714-9.
http://dx.doi.org/10.2337/db06-0921 PMID: 17327441

[219] Sun XQ, Luo YY, An LW, *et al.* Contribution of the Akt2 gene to type 2 diabetes in the Chinese Han population. Chin Med J (Engl) 2011; 124(5): 725-8.
PMID: 21518566

[220] Murdocca M, Spitalieri P, De Masi C, *et al.* Functional analysis of *POLD1* p.ser605del variant: The aging phenotype of MDPL syndrome is associated with an impaired DNA repair capacity. Aging (Albany NY) 2021; 13(4): 4926-45.
http://dx.doi.org/10.18632/aging.202680 PMID: 33618333

[221] Speckman RA, Garg A, Du F, *et al.* Mutational and haplotype analyses of families with familial partial lipodystrophy (Dunnigan variety) reveal recurrent missense mutations in the globular C-terminal domain of lamin A/C. Am J Hum Genet 2000; 66(4): 1192-8.
http://dx.doi.org/10.1086/302836 PMID: 10739751

[222] Cao H, Hegele RA. Nuclear lamin A/C R482Q mutation in Canadian kindreds with Dunnigan-type familial partial lipodystrophy. Hum Mol Genet 2000; 9(1): 109-12.
http://dx.doi.org/10.1093/hmg/9.1.109 PMID: 10587585

[223] Vantyghem MC, Pigny P, Maurage CA, *et al.* Patients with familial partial lipodystrophy of the Dunnigan type due to a LMNA R482W mutation show muscular and cardiac abnormalities. J Clin Endocrinol Metab 2004; 89(11): 5337-46.
http://dx.doi.org/10.1210/jc.2003-031658 PMID: 15531479

[224] Pandey SN, Pungavkar SA, Vaidya RA, *et al.* An imaging study of body composition including lipodeposition pattern in a patient of familial partial lipodystrophy (Dunnigan type). J Assoc Physicians India 2005; 53: 897-900.
PMID: 16459536

[225] Monteiro L, Foss-Freitas M, Montenegro RM, Foss M. Body fat distribution in women with familial partial lipodystrophy caused by mutation in the lamin A/C gene. Indian J Endocrinol Metab 2012; 16(1): 136-8.
http://dx.doi.org/10.4103/2230-8210.91209 PMID: 22276265

[226] Wong SPY, Huda M, English P, *et al.* Adipokines and the insulin resistance syndrome in familial partial lipodystrophy caused by a mutation in lamin A/C. Diabetologia 2005; 48(12): 2641-9.
http://dx.doi.org/10.1007/s00125-005-0038-x PMID: 16320084

[227] Haque WA, Vuitch F, Garg A. Post-mortem findings in familial partial lipodystrophy, Dunnigan variety. Diabet Med 2002; 19(12): 1022-5.
http://dx.doi.org/10.1046/j.1464-5491.2002.00796.x PMID: 12647844

[228] Lüdtke A, Roos GM, van Hettinga M, Horst BAJ, Worman HJ, Schmidt HHJ. Post-mortem findings in Dunnigan-type familial partial lipodystrophy. Diabet Med 2010; 27(2): 245-6.
http://dx.doi.org/10.1111/j.1464-5491.2009.02909.x PMID: 20546275

[229] Subramanyam L, Simha V, Garg A. Overlapping syndrome with familial partial lipodystrophy, Dunnigan variety and cardiomyopathy due to amino-terminal heterozygous missense lamin A/C mutations. Clin Genet 2010; 78(1): 66-73.
http://dx.doi.org/10.1111/j.1399-0004.2009.01350.x PMID: 20041886

[230] Owen KR, Donohoe M, Ellard S, *et al.* Mesangiocapillary glomerulonephritis type 2 associated with familial partial lipodystrophy (Dunnigan-Kobberling syndrome). Nephron Clin Pract 2004; 96(2): c35-8.
http://dx.doi.org/10.1159/000076396 PMID: 14988595

[231] Imachi H, Murao K, Ohtsuka S, *et al.* A case of Dunnigan-type familial partial lipodystrophy (FPLD) due to lamin A/C (LMNA) mutations complicated by end-stage renal disease. Endocrine 2009; 35(1): 18-21.
http://dx.doi.org/10.1007/s12020-008-9127-1 PMID: 19011997

[232] Thong KM, Xu Y, Cook J, *et al.* Cosegregation of focal segmental glomerulosclerosis in a family with familial partial lipodystrophy due to a mutation in LMNA. Nephron Clin Pract 2013; 124(1-2): 31-7.
http://dx.doi.org/10.1159/000354716 PMID: 24080738

[233] Fountas A, Giotaki Z, Dounousi E, *et al.* Familial partial lipodystrophy and proteinuric renal disease due to a missense c.1045C > T *LMNA* mutation. Endocrinol Diabetes Metab Case Rep 2017; 2017: 0049.
http://dx.doi.org/10.1530/EDM-17-0049 PMID: 28620495

[234] Soyaltin UE, Simsir IY, Akinci B, *et al.* Homozygous LMNA p.R582H pathogenic variant reveals increasing effect on the severity of fat loss in lipodystrophy. Clin Diabetes Endocrinol 2020; 6: 13.

[235] Agarwal AK, Fryns JP, Auchus RJ, Garg A. Zinc metalloproteinase, ZMPSTE24, is mutated in mandibuloacral dysplasia. Hum Mol Genet 2003; 12(16): 1995-2001.
http://dx.doi.org/10.1093/hmg/ddg213 PMID: 12913070

[236] Hitzert MM, van der Crabben SN, Baldewsingh G, *et al.* Mandibuloacral dysplasia type B (MADB): A cohort of eight patients from Suriname with a homozygous founder mutation in ZMPSTE24 (FACE1), clinical diagnostic criteria and management guidelines. Orphanet J Rare Dis 2019; 14(1): 294.
http://dx.doi.org/10.1186/s13023-019-1269-0 PMID: 31856865

[237] Freidenberg GR, Cutler DL, Jones MC, *et al.* Severe insulin resistance and diabetes mellitus in mandibuloacral dysplasia. Arch Pediatr Adolesc Med 1992; 146(1): 93-9.
http://dx.doi.org/10.1001/archpedi.1992.02160130095028
PMID: 1736653

[238] Epstkin CJ, Martin GM, Schultz AL, Motulskys AG. Werner's syndrome a review of its symptomatology, natural history, pathologic features, genetics and relationship to the natural aging process. Medicine (Baltimore) 1966; 45(3): 177-221.
http://dx.doi.org/10.1097/00005792-196605000-00001 PMID: 5327241

[239] Peng H, Wang J, Liu Y, *et al.* Case Report: A novel *WRN* mutation in Werner syndrome patient with diabetic foot disease and myelodysplastic syndrome. Front Endocrinol (Lausanne) 2022; 13: 918979.
http://dx.doi.org/10.3389/fendo.2022.918979 PMID: 35909544

[240] Lauper JM, Krause A, Vaughan TL, Monnat RJ Jr. Spectrum and risk of neoplasia in Werner syndrome: A systematic review. PLoS One 2013; 8(4): e59709.
http://dx.doi.org/10.1371/journal.pone.0059709 PMID: 23573208

[241] Smith U, Digirolamo M, Blohmé G, Kral JG, Tisell LE. Possible systemic metabolic effects of regional adiposity in a patient with Werner's syndrome. Int J Obes 1980; 4(2): 153-63.
PMID: 6995362

[242] Mori S, Murano S, Yokote K, *et al.* Enhanced intra-abdominal visceral fat accumulation in patients with Werner's syndrome. Int J Obes 2001; 25(2): 292-5.

http://dx.doi.org/10.1038/sj.ijo.0801529 PMID: 11410834
[243] Yokote K, Honjo S, Kobayashi K, *et al.* Metabolic improvement and abdominal fat redistribution in Werner syndrome by pioglitazone. J Am Geriatr Soc 2004; 52(9): 1582-3. http://dx.doi.org/10.1111/j.1532-5415.2004.52430_4.x PMID: 15341572
[244] Honjo S, Yokote K, Fujishiro T, *et al.* Early amelioration of insulin resistance and reduction of interleukin-6 in Werner syndrome using pioglitazone. J Am Geriatr Soc 2008; 56(1): 173-4. http://dx.doi.org/10.1111/j.1532-5415.2007.01484.x PMID: 18184212
[245] Blohmé G, Smith U. Metabolic studies in a case of Werner's syndrome. Diabete Metab 1979; 5(2): 119-24. PMID: 478081
[246] Yamada K, Ikegami H, Yoneda H, Miki T, Ogihara T. All patients with Werner's syndrome are insulin resistant, but only those who also have impaired insulin secretion develop overt diabetes. Diabetes Care 1999; 22(12): 2094-5. http://dx.doi.org/10.2337/diacare.22.12.2094 PMID: 10587857
[247] Abe T, Yamaguchi Y, Izumino K, *et al.* Evaluation of insulin response in glucose tolerance test in a patient with Werner's syndrome: A 16-year follow-up study. Diabetes Nutr Metab 2000; 13(2): 113-8. PMID: 10898130
[248] Okabe E, Takemoto M, Onishi S, *et al.* Incidence and characteristics of metabolic disorders and vascular complications in individuals with Werner syndrome in Japan. J Am Geriatr Soc 2012; 60(5): 997-8. http://dx.doi.org/10.1111/j.1532-5415.2012.03944.x PMID: 22587870
[249] Takemoto M, Kubota Y, Taniguchi T, *et al.* Management guideline for Werner syndrome. Diabetes associated with Werner syndrome. Geriatr Gerontol Int 2021; 21(2): 142-5. http://dx.doi.org/10.1111/ggi.14083 PMID: 33169495
[250] Atallah I, McCormick D, Good JM, *et al.* Partial lipodystrophy, severe dyslipidaemia and insulin resistant diabetes as early signs of Werner syndrome. J Clin Lipidol 2022; 16(5): 583-90. http://dx.doi.org/10.1016/j.jacl.2022.06.004 PMID: 35780059
[251] Wang X, Liu S, Qin F, Liu Q, Wang Q. Werner syndrome presenting as early-onset diabetes: A case report. J Diabetes Investig 2022; 13(3): 592-8. http://dx.doi.org/10.1111/jdi.13682
[252] Watanabe K, Kobayashi K, Takemoto M, *et al.* Sitagliptin improves postprandial hyperglycemia by inhibiting glucagon secretion in Werner syndrome with diabetes. Diabetes Care 2013; 36(8): e119. http://dx.doi.org/10.2337/dc13-0709 PMID: 23881973
[253] Yamaga M, Takemoto M, Shoji M, *et al.* Werner syndrome: A model for sarcopenia due to accelerated aging. Aging 2017; 9(7): 1738-44. http://dx.doi.org/10.18632/aging.101265 PMID: 28738022
[254] Tanaka F, Kuzuya M. Examination of the body composition of patients with Werner syndrome using bioelectrical impedance analysis. Geriatr Gerontol Int 2022; 22(1): 75-80. http://dx.doi.org/10.1111/ggi.14310 PMID: 34841636
[255] Weedon MN, Ellard S, Prindle MJ, *et al.* An in-frame deletion at the polymerase active site of POLD1 causes a multisystem disorder with lipodystrophy. Nat Genet 2013; 45(8): 947-50. http://dx.doi.org/10.1038/ng.2670 PMID: 23770608
[256] Gladys B, René W, Anabelle D, *et al.* Child to adulthood clinical description of MDPL syndrome due to a novel variant in POLD1. Eur J Med Genet 2021; 64(12): 104333. http://dx.doi.org/10.1016/j.ejmg.2021.104333 PMID: 34517090
[257] Bappy MNI, Roy A, Rabbi MGR, *et al.* Scrutinizing Deleterious Nonsynonymous SNPs and Their Effect on Human POLD1 Gene. Genet Res 2022; 2022: 1-12. http://dx.doi.org/10.1155/2022/1740768 PMID: 35620275
[258] Kamath-Loeb AS, Johansson E, Burgers PMJ, Loeb LA. Functional interaction between the Werner Syndrome protein and DNA polymerase δ. Proc Natl Acad Sci USA 2000; 97(9): 4603-8. http://dx.doi.org/10.1073/pnas.97.9.4603 PMID: 10781066
[259] Kamath-Loeb AS, Shen JC, Schmitt MW, Loeb LA. The Werner syndrome exonuclease facilitates DNA degradation and high fidelity DNA polymerization by human DNA polymerase δ. J Biol Chem 2012; 287(15): 12480-90. http://dx.doi.org/10.1074/jbc.M111.332577 PMID: 22351772
[260] Chen T, Li M, Wu H, *et al.* Short stature as the first manifestation of mandibular hypoplasia, deafness, progeroid feature and lipodystrophy (MDPL) syndrome. Int J Clin Exp Med 2017; 10(2): 3876-83.
[261] Elouej S, Beleza-Meireles A, Caswell R, *et al.* Exome sequencing reveals a de novo POLD1 mutation causing phenotypic variability in mandibular hypoplasia, deafness, progeroid features, and lipodystrophy syndrome (MDPL). Metabolism 2017; 71: 213-25. http://dx.doi.org/10.1016/j.metabol.2017.03.011 PMID: 28521875
[262] Shastry S, Simha V, Godbole K, *et al.* A novel syndrome of mandibular hypoplasia, deafness, and progeroid features associated with lipodystrophy, undescended testes, and male hypogonadism. J Clin Endocrinol Metab 2010; 95(10): E192-7. http://dx.doi.org/10.1210/jc.2010-0419 PMID: 20631028
[263] Sasaki H, Yanagi K, Ugi S, *et al.* Definitive diagnosis of mandibular hypoplasia, deafness, progeroid features and lipodystrophy (MDPL) syndrome caused by a recurrent de novo mutation in the POLD1 gene. Endocr J 2018; 65(2): 227-38. http://dx.doi.org/10.1507/endocrj.EJ17-0287 PMID: 29199204
[264] German J, Sanz MM, Ciocci S, Ye TZ, Ellis NA. Syndrome-causing mutations of the *BLM* gene in persons in the Bloom's Syndrome Registry. Hum Mutat 2007; 28(8): 743-53. http://dx.doi.org/10.1002/humu.20501 PMID: 17407155
[265] Gönenc II, Elcioglu NH, Martinez Grijalva C, *et al.* Phenotypic spectrum of*BLM* - and*RMI1* -related Bloom syndrome. Clin Genet 2022; 101(5-6): 559-64. http://dx.doi.org/10.1111/cge.14125 PMID: 35218564
[266] Bloom D. Congenital telangiectatic erythema resembling lupus erythematosus in dwarfs; probably a syndrome entity. AMA Am J Dis Child 1954; 88(6): 754-8. http://dx.doi.org/10.1001/archpedi.1954.02050100756008 PMID: 13206391
[267] Diaz A, Vogiatzi MG, Sanz MM, German J. Evaluation of short stature, carbohydrate metabolism and other endocrinopathies in Bloom's syndrome. Horm Res Paediatr 2006; 66(3): 111-7. http://dx.doi.org/10.1159/000093826 PMID: 16763388
[268] Farhan SMK, Robinson JF, McIntyre AD, *et al.* A novel LIPE nonsense mutation found using exome sequencing in siblings with late-onset familial partial lipodystrophy. Can J Cardiol 2014; 30(12): 1649-54. http://dx.doi.org/10.1016/j.cjca.2014.09.007 PMID: 25475467
[269] Garg A, Sankella S, Xing C, Agarwal AK. Whole-exome sequencing identifies *ADRA2A* mutation in atypical familial partial lipodystrophy. JCI Insight 2016; 1(9): e86870. http://dx.doi.org/10.1172/jci.insight.86870 PMID: 27376152
[270] Rubio-Cabezas O, Puri V, Murano I, *et al.* Partial lipodystrophy and insulin resistant diabetes in a patient with a homozygous nonsense mutation in *CIDEC*. EMBO Mol Med 2009; 1(5): 280-7. http://dx.doi.org/10.1002/emmm.200900037 PMID: 20049731
[271] Ito M, Nagasawa M, Hara T, Ide T, Murakami K. Differential roles of CIDEA and CIDEC in insulin-induced anti-apoptosis and lipid droplet formation in human adipocytes. J Lipid Res 2010; 51(7): 1676-84. http://dx.doi.org/10.1194/jlr.M002147 PMID: 20154362
[272] Ito M, Nagasawa M, Omae N, Ide T, Akasaka Y, Murakami K. Differential regulation of CIDEA and CIDEC expression by insulin *via* Akt1/2- and JNK2-dependent pathways in human adipocytes. J Lipid Res 2011; 52(8): 1450-60. http://dx.doi.org/10.1194/jlr.M012427 PMID: 21636835
[273] Gandotra S, Le Dour C, Bottomley W, *et al.* Perilipin deficiency and autosomal dominant partial lipodystrophy. N Engl J Med 2011; 364(8): 740-8. http://dx.doi.org/10.1056/NEJMoa1007487 PMID: 21345103
[274] Kozusko K, Tsang VHM, Bottomley W, *et al.* Clinical and molecular characterization of a novel PLIN1 frameshift mutation identified in patients with familial partial lipodystrophy. Diabetes 2015; 64(1): 299-310. http://dx.doi.org/10.2337/db14-0104 PMID: 25114292

[275] Laver TW, Patel KA, Colclough K, *et al.* PLIN1 haploinsufficiency is not associated with lipodystrophy. J Clin Endocrinol Metab 2018; 103(9): 3225-30. http://dx.doi.org/10.1210/jc.2017-02662 PMID: 30020498

[276] Patel KA, Burman S, Laver TW, Hattersley AT, Frayling TM, Weedon MN. *PLIN1* haploinsufficiency causes a favorable metabolic profile. J Clin Endocrinol Metab 2022; 107(6): e2318-23. http://dx.doi.org/10.1210/clinem/dgac104 PMID: 35235652

[277] Graul-Neumann LM, Kienitz T, Robinson PN, *et al.* Marfan syndrome with neonatal progeroid syndrome-like lipodystrophy associated with a novel frameshift mutation at the 3′ terminus of the FBN1-gene. Am J Med Genet A 2010; 152A(11): 2749-55. http://dx.doi.org/10.1002/ajmg.a.33690 PMID: 20979188

[278] Horn D, Robinson PN. Progeroid facial features and lipodystrophy associated with a novel splice site mutation in the final intron of the FBN1 gene. Am J Med Genet A 2011; 155(4): 721-4. http://dx.doi.org/10.1002/ajmg.a.33905 PMID: 21594993

[279] Goldblatt J, Hyatt J, Edwards C, Walpole I. Further evidence for a marfanoid syndrome with neonatal progeroid features and severe generalized lipodystrophy due to frameshift mutations near the 3′ end of the FBN1 gene. Am J Med Genet A 2011; 155(4): 717-20. http://dx.doi.org/10.1002/ajmg.a.33906 PMID: 21594992

[280] Takenouchi T, Hida M, Sakamoto Y, *et al.* Severe congenital lipodystrophy and a progeroid appearance: Mutation in the penultimate exon of *FBN1* causing a recognizable phenotype. Am J Med Genet A 2013; 161(12): 3057-62. http://dx.doi.org/10.1002/ajmg.a.36157 PMID: 24039054

[281] Garg A, Xing C. De novo heterozygous *FBN1* mutations in the extreme C-terminal region cause progeroid fibrillinopathy. Am J Med Genet A 2014; 164(5): 1341-5. http://dx.doi.org/10.1002/ajmg.a.36449 PMID: 24665001

[282] Passarge E, Robinson PN, Graul-Neumann LM. Marfanoid–progeroid–lipodystrophy syndrome: A newly recognized fibrillinopathy. Eur J Hum Genet 2016; 24(9): 1244-7. http://dx.doi.org/10.1038/ejhg.2016.6 PMID: 26860060

[283] Boden G, Chen X, Mozzoli M, Ryan I. Effect of fasting on serum leptin in normal human subjects. J Clin Endocrinol Metab 1996; 81(9): 3419-23. http://dx.doi.org/10.1210/jcem.81.9.8784108 PMID: 8784108

[284] Considine RV, Sinha MK, Heiman ML, *et al.* Serum immunoreactive-leptin concentrations in normal-weight and obese humans. N Engl J Med 1996; 334(5): 292-5. http://dx.doi.org/10.1056/NEJM199602013340503 PMID: 8532024

[285] Larsson H, Elmståhl S, Ahrén B. Plasma leptin levels correlate to islet function independently of body fat in postmenopausal women. Diabetes 1996; 45(11): 1580-4. http://dx.doi.org/10.2337/diab.45.11.1580 PMID: 8866564

[286] Al-Shoumer KAS, Anyaoku V, Richmond W, Johnston DG. Elevated leptin concentrations in growth hormone-deficient hypopituitary adults. Clin Endocrinol (Oxf) 1997; 47(2): 153-9. http://dx.doi.org/10.1046/j.1365-2265.1997.2131054.x PMID: 9302387

[287] Kolaczynski JW, Considine RV, Ohannesian J, *et al.* Responses of leptin to short-term fasting and refeeding in humans: A link with ketogenesis but not ketones themselves. Diabetes 1996; 45(11): 1511-5. http://dx.doi.org/10.2337/diab.45.11.1511 PMID: 8866554

[288] Sinha MK, Opentanova I, Ohannesian JP, *et al.* Evidence of free and bound leptin in human circulation. Studies in lean and obese subjects and during short-term fasting. J Clin Invest 1996; 98(6): 1277-82. http://dx.doi.org/10.1172/JCI118913 PMID: 8823291

[289] Hernández C, Simó R, Chacón P, *et al.* Influence of surgical stress and parenteral nutrition on serum leptin concentration. Clin Nutr 2000; 19(1): 61-4. http://dx.doi.org/10.1054/clnu.1999.0075 PMID: 10700536

[290] Dubuc GR, Phinney SD, Stern JS, Havel PJ. Changes of serum leptin and endocrine and metabolic parameters after 7 days of energy restriction in men and women. Metabolism 1998; 47(4): 429-34. http://dx.doi.org/10.1016/S0026-0495(98)90055-5 PMID: 9550541

[291] Kolaczynski JW, Ohannesian JP, Considine RV, Marco CC, Caro JF. Response of leptin to short-term and prolonged overfeeding in humans. J Clin Endocrinol Metab 1996; 81(11): 4162-5. http://dx.doi.org/10.1210/jcem.81.11.8923877 PMID: 8923877

[292] Montague CT, Farooqi IS, Whitehead JP, *et al.* Congenital leptin deficiency is associated with severe early-onset obesity in humans. Nature 1997; 387(6636): 903-8. http://dx.doi.org/10.1038/43185 PMID: 9202122

[293] Strobel A, Issad T, Camoin L, Ozata M, Strosberg AD. A leptin missense mutation associated with hypogonadism and morbid obesity. Nat Genet 1998; 18(3): 213-5. http://dx.doi.org/10.1038/ng0398-213 PMID: 9500540

[294] Gibson WT, Farooqi IS, Moreau M, *et al.* Congenital leptin deficiency due to homozygosity for the Delta133G mutation: Report of another case and evaluation of response to four years of leptin therapy. J Clin Endocrinol Metab 2004; 89(10): 4821-6. http://dx.doi.org/10.1210/jc.2004-0376 PMID: 15472169

[295] Mazen I, Amr K, Tantawy S, Farooqi IS, El Gammal M. A novel mutation in the leptin gene (W121X) in an Egyptian family. Mol Genet Metab Rep 2014; 1: 474-6. http://dx.doi.org/10.1016/j.ymgmr.2014.10.002 PMID: 27896126

[296] Ozsu E, Ceylaner S, Onay H. Early-onset severe obesity due to complete deletion of the leptin gene in a boy. J Pediatr Endocrinol Metab 2017; 30(11): 1227-30. http://dx.doi.org/10.1515/jpem-2017-0063 PMID: 29040067

[297] Yupanqui-Lozno H, Bastarrachea RA, Yupanqui-Velazco ME, *et al.* Congenital leptin deficiency and leptin gene missense mutation found in two colombian sisters with severe obesity. Genes (Basel) 2019; 10(5): 342. http://dx.doi.org/10.3390/genes10050342 PMID: 31067764

[298] Fırat SN, Onay H. Early-onset severe obesity due to homozygous p.R105W (c313C> T) mutation in leptin gene in Turkish siblings: Two cases reports. Obes Res Clin Pract 2021; 15(6): 600-3. http://dx.doi.org/10.1016/j.orcp.2021.11.001 PMID: 34802983

[299] Wabitsch M, Funcke JB, Lennerz B, *et al.* Biologically inactive leptin and early-onset extreme obesity. N Engl J Med 2015; 372(1): 48-54. http://dx.doi.org/10.1056/NEJMoa1406653 PMID: 25551525

[300] Heymsfield SB, Fong TM, Gantz I, Erondu N. Fat and energy partitioning: Longitudinal observations in leptin-treated adults homozygous for a Lep mutation. Obesity (Silver Spring) 2006; 14(2): 258-65. http://dx.doi.org/10.1038/oby.2006.33 PMID: 16571851

[301] Fischer-Posovszky P, von Schnurbein J, Moepps B, *et al.* A new missense mutation in the leptin gene causes mild obesity and hypogonadism without affecting T cell responsiveness. J Clin Endocrinol Metab 2010; 95(6): 2836-40. http://dx.doi.org/10.1210/jc.2009-2466 PMID: 20382689

[302] Farooqi IS, Jebb SA, Langmack G, *et al.* Effects of recombinant leptin therapy in a child with congenital leptin deficiency. N Engl J Med 1999; 341(12): 879-84. http://dx.doi.org/10.1056/NEJM199909163411204 PMID: 10486419

[303] Licinio J, Caglayan S, Ozata M, *et al.* Phenotypic effects of leptin replacement on morbid obesity, diabetes mellitus, hypogonadism, and behavior in leptin-deficient adults. Proc Natl Acad Sci USA 2004; 101(13): 4531-6. http://dx.doi.org/10.1073/pnas.0308767101 PMID: 15070752

[304] Farooqi IS, Matarese G, Lord GM, *et al.* Beneficial effects of leptin on obesity, T cell hyporesponsiveness, and neuroendocrine/metabolic dysfunction of human congenital leptin deficiency. J Clin Invest 2002; 110(8): 1093-103. http://dx.doi.org/10.1172/JCI0215693 PMID: 12393845

[305] Mazen I, El-Gammal M, Abdel-Hamid M, Amr K. A novel homozygous missense mutation of the leptin gene (N103K) in an obese Egyptian patient. Mol Genet Metab 2009; 97(4): 305-8. http://dx.doi.org/10.1016/j.ymgme.2009.04.002 PMID: 19427251

[306] Paz-Filho G, Mastronardi C, Delibasi T, Wong ML, Licinio J. Congenital leptin deficiency: Diagnosis and effects of leptin replacement therapy. Arq Bras Endocrinol Metabol 2010; 54(8): 690-7. http://dx.doi.org/10.1590/S0004-27302010000800005 PMID: 21340154

[307] von Schnurbein J, Heni M, Moss A, *et al.* Rapid improvement of hepatic steatosis after initiation of leptin substitution in a leptin-deficient girl. Horm Res Paediatr 2013; 79(5): 310-7. http://dx.doi.org/10.1159/000348541 PMID: 23651953

[308] Brandt S, von Schnurbein J, Denzer C, Kratzer W, Wabitsch M. Lower circulating leptin levels are related to non-alcoholic fatty liver disease in children with obesity. Front Endocrinol (Lausanne) 2022; 13: 881982. http://dx.doi.org/10.3389/fendo.2022.881982 PMID: 35677722

[309] Paz-Filho GJ, Delibasi T, Erol HK, Wong ML, Licinio J. Cellular immunity before and after leptin replacement therapy. J Pediatr Endocrinol Metab 2009; 22(11): 1069-74. http://dx.doi.org/10.1515/JPEM.2009.22.11.1069 PMID: 20101893

[310] Farooqi IS, Wangensteen T, Collins S, *et al.* Clinical and molecular genetic spectrum of congenital deficiency of the leptin receptor. N Engl J Med 2007; 356(3): 237-47. http://dx.doi.org/10.1056/NEJMoa063988 PMID: 17229951

[311] Huvenne H, Le Beyec J, Pépin D, *et al.* Seven novel deleterious LEPR mutations found in early-onset obesity: A ΔExon6-8 shared by subjects from Reunion Island, France, suggests a founder effect. J Clin Endocrinol Metab 2015; 100(5): E757-66. http://dx.doi.org/10.1210/jc.2015-1036 PMID: 25751111

[312] Clément K, Vaisse C, Lahlou N, *et al.* A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. Nature 1998; 392(6674): 398-401. http://dx.doi.org/10.1038/32911 PMID: 9537324

[313] Andiran N, Çelik N, Andiran F. Homozygosity for two missense mutations in the leptin receptor gene (P316T;W646C) in a Turkmenian girl with severe early-onset obesity. J Pediatr Endocrinol Metab 2011; 24(11-12): 1043-5. http://dx.doi.org/10.1515/JPEM.2011.313 PMID: 22308862

[314] Mazen I, El-Gammal M, Abdel-Hamid M, Farooqi IS, Amr K. Homozygosity for a novel missense mutation in the leptin receptor gene (P316T) in two Egyptian cousins with severe early onset obesity. Mol Genet Metab 2011; 102(4): 461-4. http://dx.doi.org/10.1016/j.ymgme.2010.12.013 PMID: 21306929

[315] Le Beyec J, Cugnet-Anceau C, Pépin D, *et al.* Homozygous leptin receptor mutation due to uniparental disomy of chromosome 1: Response to bariatric surgery. J Clin Endocrinol Metab 2013; 98(2): E397-402. http://dx.doi.org/10.1210/jc.2012-2779 PMID: 23275530

[316] Niazi RK, Gjesing AP, Hollensted M, *et al.* Identification of novel LEPR mutations in Pakistani families with morbid childhood obesity. BMC Med Genet 2018; 19(1): 199. http://dx.doi.org/10.1186/s12881-018-0710-x PMID: 30442103

[317] Nunziata A, Funcke JB, Borck G, *et al.* Functional and phenotypic characteristics of human leptin receptor mutations. J Endocr Soc 2019; 3(1): 27-41. http://dx.doi.org/10.1210/js.2018-00123 PMID: 30560226

[318] Armağan C, Yılmaz C, Koç A, *et al.* A toddler with a novel LEPR mutation. Hormones (Athens) 2019; 18(2): 237-40. http://dx.doi.org/10.1007/s42000-019-00097-6 PMID: 30778850

[319] Zorn S, von Schnurbein J, Kohlsdorf K, Denzer C, Wabitsch M. Diagnostic and therapeutic odyssey of two patients with compound heterozygous leptin receptor deficiency. Mol Cell Pediatr 2020; 7(1): 15. http://dx.doi.org/10.1186/s40348-020-00107-3 PMID: 33140236

[320] Voigtmann F, Wolf P, Landgraf K, *et al.* Identification of a novel leptin receptor (LEPR) variant and proof of functional relevance directing treatment decisions in patients with morbid obesity. Metabolism 2021; 116: 154438. http://dx.doi.org/10.1016/j.metabol.2020.154438 PMID: 33221380

[321] Chaves C, Kay T, Anselmo J. Early onset obesity due to a mutation in the human leptin receptor gene. Endocrinol Diabetes Metab Case Rep 2022; 2022: 21-0124. http://dx.doi.org/10.1530/EDM-21-0124 PMID: 36001025

[322] Brandt S, Schnurbein J, Lennerz B, *et al.* Methylphenidate in children with monogenic obesity due to *LEPR* or *MC4R* deficiency improves feeling of satiety and reduces BMI-SDS—A case series. Pediatr Obes 2020; 15(1): e12577. http://dx.doi.org/10.1111/ijpo.12577 PMID: 31670905

[323] Clément K, van den Akker E, Argente J, *et al.* Efficacy and safety of setmelanotide, an MC4R agonist, in individuals with severe obesity due to LEPR or *POMC* deficiency: Single-arm, open-label, multicentre, phase 3 trials. Lancet Diabetes Endocrinol 2020; 8(12): 960-70. http://dx.doi.org/10.1016/S2213-8587(20)30364-8 PMID: 33137293

[324] Krude H, Biebermann H, Luck W, Horn R, Brabant G, Grüters A. Severe early-onset obesity, adrenal insufficiency and red hair pigmentation caused by *POMC* mutations in humans. Nat Genet 1998; 19(2): 155-7. http://dx.doi.org/10.1038/509 PMID: 9620771

[325] Yeo GSH, Farooqi IS, Aminian S, Halsall DJ, Stanhope RG, O'Rahilly S. A frameshift mutation in MC4R associated with dominantly inherited human obesity. Nat Genet 1998; 20(2): 111-2. http://dx.doi.org/10.1038/2404 PMID: 9771698

[326] Vaisse C, Clement K, Guy-Grand B, Froguel P. A frameshift mutation in human MC4R is associated with a dominant form of obesity. Nat Genet 1998; 20(2): 113-4. http://dx.doi.org/10.1038/2407 PMID: 9771699

[327] Farooqi IS, Yeo GSH, Keogh JM, *et al.* Dominant and recessive inheritance of morbid obesity associated with melanocortin 4 receptor deficiency. J Clin Invest 2000; 106(2): 271-9. http://dx.doi.org/10.1172/JCI9397 PMID: 10903343

[328] Kobayashi H, Ogawa Y, Shintani M, *et al.* A Novel homozygous missense mutation of melanocortin-4 receptor (MC4R) in a Japanese woman with severe obesity. Diabetes 2002; 51(1): 243-6. http://dx.doi.org/10.2337/diabetes.51.1.243 PMID: 11756348

[329] Farooqi IS, Keogh JM, Yeo GSH, Lank EJ, Cheetham T, O'Rahilly S. Clinical spectrum of obesity and mutations in the melanocortin 4 receptor gene. N Engl J Med 2003; 348(12): 1085-95. http://dx.doi.org/10.1056/NEJMoa022050 PMID: 12646665

[330] Buono P, Pasanisi F, Nardelli C, *et al.* Six novel mutations in the proopiomelanocortin and melanocortin receptor 4 genes in severely obese adults living in southern Italy. Clin Chem 2005; 51(8): 1358-64. http://dx.doi.org/10.1373/clinchem.2005.047886 PMID: 15951321

[331] Dubern B, Bisbis S, Talbaoui H, *et al.* Homozygous null mutation of the melanocortin-4 receptor and severe early-onset obesity. J Pediatr 2007; 150(6): 613-7. http://dx.doi.org/10.1016/j.jpeds.2007.01.041

[332] Martinelli CE, Keogh JM, Greenfield JR, *et al.* Obesity due to melanocortin 4 receptor (MC4R) deficiency is associated with increased linear growth and final height, fasting hyperinsulinemia, and incompletely suppressed growth hormone secretion. J Clin Endocrinol Metab 2011; 96(1): E181-8. http://dx.doi.org/10.1210/jc.2010-1369 PMID: 21047921

[333] Thearle MS, Muller YL, Hanson RL, *et al.* Greater impact of melanocortin-4 receptor deficiency on rates of growth and risk of type 2 diabetes during childhood compared with adulthood in Pima Indians. Diabetes 2012; 61(1): 250-7. http://dx.doi.org/10.2337/db11-0708 PMID: 22106157

[334] Vaisse C, Clement K, Durand E, Hercberg S, Guy-Grand B, Froguel P. Melanocortin-4 receptor mutations are a frequent and heterogeneous cause of morbid obesity. J Clin Invest 2000; 106(2): 253-62. http://dx.doi.org/10.1172/JCI9238 PMID: 10903341

[335] Lubrano-Berthelier C, Dubern B, Lacorte JM, *et al.* Melanocortin 4 receptor mutations in a large cohort of severely obese adults: Prevalence, functional classification, genotype-phenotype relationship, and lack of association with binge eating. J Clin Endocrinol Metab 2006; 91(5): 1811-8. http://dx.doi.org/10.1210/jc.2005-1411 PMID: 16507637

[336] Lubrano-Berthelier C, Le Stunff C, Bougnères P, Vaisse C. A homozygous null mutation delineates the role of the melanocortin-4 receptor in humans. J Clin Endocrinol Metab 2004; 89(5): 2028-32. http://dx.doi.org/10.1210/jc.2003-031993 PMID: 15126516

[337] Collet TH, Dubern B, Mokrosinski J, *et al.* Evaluation of a melanocortin-4 receptor (MC4R) agonist (Setmelanotide) in MC4R deficiency. Mol Metab 2017; 6(10): 1321-9. http://dx.doi.org/10.1016/j.molmet.2017.06.015 PMID: 29031731

[338] Fojas EGF, Radha SK, Ali T, Nadler EP, Lessan N. Weight and glycemic control outcomes of bariatric surgery and pharmacothera-

py in patients with melanocortin-4 receptor deficiency. Front Endocrinol (Lausanne) 2022; 12: 792354.
http://dx.doi.org/10.3389/fendo.2021.792354 PMID: 35095762

[339] Cooiman MI, Alsters SIM, Duquesnoy M, *et al.* Long-term weight outcome after bariatric surgery in patients with melanocortin-4 receptor gene variants: A Case–Control Study of 105 Patients. Obes Surg 2022; 32(3): 837-44.
http://dx.doi.org/10.1007/s11695-021-05869-x PMID: 34984630

[340] Geller F, Reichwald K, Dempfle A, *et al.* Melanocortin-4 receptor gene variant I103 is negatively associated with obesity. Am J Hum Genet 2004; 74(3): 572-81.
http://dx.doi.org/10.1086/382490 PMID: 14973783

[341] Stutzmann F, Vatin V, Cauchi S, *et al.* Non-synonymous polymorphisms in melanocortin-4 receptor protect against obesity: The two facets of a Janus obesity gene. Hum Mol Genet 2007; 16(15): 1837-44.
http://dx.doi.org/10.1093/hmg/ddm132 PMID: 17519222

[342] Krude H, Biebermann H, Schnabel D, *et al.* Obesity due to proopiomelanocortin deficiency: Three new cases and treatment trials with thyroid hormone and ACTH4-10. J Clin Endocrinol Metab 2003; 88(10): 4633-40.
http://dx.doi.org/10.1210/jc.2003-030502 PMID: 14557433

[343] Clément K, Dubern B, Mencarelli M, *et al.* Unexpected endocrine features and normal pigmentation in a young adult patient carrying a novel homozygous mutation in the *POMC* gene. J Clin Endocrinol Metab 2008; 93(12): 4955-62.
http://dx.doi.org/10.1210/jc.2008-1164 PMID: 18765507

[344] Darcan S, Can S, Goksen D, Asar G. Transient salt wasting in *POMC*-deficiency due to infection induced stress. Exp Clin Endocrinol Diabetes 2010; 118(4): 281-3.
http://dx.doi.org/10.1055/s-0029-1241203 PMID: 19998238

[345] Mendiratta MS, Yang Y, Balazs AE, *et al.* Early onset obesity and adrenal insufficiency associated with a homozygous *POMC* mutation. Int J Pediatr Endocrinol 2011; 2011(1): 5.
http://dx.doi.org/10.1186/1687-9856-2011-5 PMID: 21860632

[346] Cirillo G, Marini R, Ito S, *et al.* Lack of red hair phenotype in a North-African obese child homozygous for a novel *POMC* null mutation: Nonsense-mediated decay RNA evaluation and hair pigment chemical analysis. Br J Dermatol 2012; 167(6): 1393-5.
http://dx.doi.org/10.1111/j.1365-2133.2012.11060.x PMID: 22612534

[347] Hung CN, Poon WT, Lee CY, Law CY, Chan AYW. A case of early-onset obesity, hypocortisolism, and skin pigmentation problem due to a novel homozygous mutation in the proopiomelanocortin (*POMC*) gene in an Indian boy. J Pediatr Endocrinol Metab 2012; 25(1-2): 175-9.
http://dx.doi.org/10.1515/jpem-2011-0437 PMID: 22570972

[348] Ozen S, Aldemir O. Early-onset severe obesity with ACTH deficiency and red hair in a boy: The *POMC* deficiency. Genet Couns 2012; 23(4): 493-5.
PMID: 23431750

[349] Aslan IR, Ranadive SA, Valle I, Kollipara S, Noble JA, Vaisse C. The melanocortin system and insulin resistance in humans: Insights from a patient with complete *POMC* deficiency and type 1 diabetes mellitus. Int J Obes 2014; 38(1): 148-51.
http://dx.doi.org/10.1038/ijo.2013.53 PMID: 23649472

[350] Ozsu E, Bahm A. Delayed diagnosis of proopiomelanocortin (*POMC*) deficiency with type 1 diabetes in a 9-year-old girl and her infant sibling. J Pediatr Endocrinol Metab 2017; 30(10): 1137-40.
http://dx.doi.org/10.1515/jpem-2017-0064 PMID: 28915118

[351] Hilado MA, Randhawa RS. A novel mutation in the proopiomelanocortin (*POMC*) gene of a Hispanic child: Metformin treatment shows a beneficial impact on the body mass index. J Pediatr Endocrinol Metab 2018; 31(7): 815-9.
http://dx.doi.org/10.1515/jpem-2017-0467 PMID: 29858905

[352] Çetinkaya S, Güran T, Kurnaz E, *et al.* A Patient with Proopiomelanocortin Deficiency: An Increasingly Important Diagnosis to Make. J Clin Res Pediatr Endocrinol 2018; 10(1): 68-73.
http://dx.doi.org/10.4274/jcrpe.4638 PMID: 28739551

[353] Graves LE, Khouri JM, Kristidis P, Verge CF. Proopiomelanocortin deficiency diagnosed in infancy in two boys and a review of the known cases. J Paediatr Child Health 2021; 57(4): 484-90.
http://dx.doi.org/10.1111/jpc.15407 PMID: 33666293

[354] Gregoric N, Groselj U, Bratina N, *et al.* Two cases with an early presented proopiomelanocortin deficiency—A long-term follow-up and systematic literature review. front endocrinol (Lausanne) 2021; 12: 689387.
http://dx.doi.org/10.3389/fendo.2021.689387 PMID: 34177811

[355] Farooqi IS, Drop S, Clements A, *et al.* Heterozygosity for a *POMC*-null mutation and increased obesity risk in humans. Diabetes 2006; 55(9): 2549-53.
http://dx.doi.org/10.2337/db06-0214 PMID: 16936203

[356] Hearn T, Spalluto C, Phillips VJ, *et al.* Subcellular localization of ALMS1 supports involvement of centrosome and basal body dysfunction in the pathogenesis of obesity, insulin resistance, and type 2 diabetes. Diabetes 2005; 54(5): 1581-7.
http://dx.doi.org/10.2337/diabetes.54.5.1581 PMID: 15855349

[357] Knorz VJ, Spalluto C, Lessard M, *et al.* Centriolar association of ALMS1 and likely centrosomal functions of the ALMS motif-containing proteins C10orf90 and KIAA1731. Mol Biol Cell 2010; 21(21): 3617-29.
http://dx.doi.org/10.1091/mbc.e10-03-0246 PMID: 20844083

[358] Marshall JD, Maffei P, Collin GB, Naggert JK. Alström syndrome: Genetics and clinical overview. Curr Genomics 2011; 12(3): 225-35.
http://dx.doi.org/10.2174/138920211795677912 PMID: 22043170

[359] Leitch CC, Lodh S, Prieto-Echagüe V, Badano JL, Zaghloul NA. Basal body proteins regulate Notch signaling *via* endosomal trafficking. J Cell Sci 2014; 127(Pt 11): jcs.130344.
http://dx.doi.org/10.1242/jcs.130344 PMID: 24681783

[360] Marshall JD, Bronson RT, Collin GB, *et al.* New Alström syndrome phenotypes based on the evaluation of 182 cases. Arch Intern Med 2005; 165(6): 675-83.
http://dx.doi.org/10.1001/archinte.165.6.675 PMID: 15795345

[361] Jatti K, Paisey R, More R. Coronary artery disease in Alström syndrome. Eur J Hum Genet 2012; 20(1): 117-8.
http://dx.doi.org/10.1038/ejhg.2011.168 PMID: 21897446

[362] Han JC, Reyes-Capo DP, Liu CY, *et al.* Comprehensive endocrine-metabolic evaluation of patients with alström syndrome compared with BMI-matched controls. J Clin Endocrinol Metab 2018; 103(7): 2707-19.
http://dx.doi.org/10.1210/jc.2018-00496 PMID: 29718281

[363] Satman I, Yılmaz MT, Gürsoy N, *et al.* Evaluation of insulin resistant diabetes mellitus in Alström syndrome: A long-term prospective follow-up of three siblings. Diabetes Res Clin Pract 2002; 56(3): 189-96.
http://dx.doi.org/10.1016/S0168-8227(02)00004-9 PMID: 11947966

[364] Minton JAL, Owen KR, Ricketts CJ, *et al.* Syndromic obesity and diabetes: Changes in body composition with age and mutation analysis of ALMS1 in 12 United Kingdom kindreds with Alstrom syndrome. J Clin Endocrinol Metab 2006; 91(8): 3110-6.
http://dx.doi.org/10.1210/jc.2005-2633 PMID: 16720663

[365] Pirgon O, Atabek ME, Tanju IA. Metabolic syndrome features presenting in early childhood in Alström syndrome: A case report. J Clin Res Pediatr Endocrinol 2009; 1(6): 278-80.
http://dx.doi.org/10.4274/jcrpe.v1i6.278 PMID: 21274310

[366] Romano S, Maffei P, Bettini V, *et al.* Alström syndrome is associated with short stature and reduced GH reserve. Clin Endocrinol (Oxf) 2013; 79(4): 529-36.
http://dx.doi.org/10.1111/cen.12180 PMID: 23445176

[367] Paisey RB, Hodge D, Williams K. Body fat distribution, serum glucose, lipid and insulin response to meals in Alström syndrome. J Hum Nutr Diet 2008; 21(3): 268-74.
http://dx.doi.org/10.1111/j.1365-277X.2008.00866.x PMID: 18477182

[368] Mokashi A, Cummings EA. Presentation and course of diabetes in children and adolescents with Alstrom syndrome. Pediatr Diabetes 2011; 12(3pt2): 270-5.
http://dx.doi.org/10.1111/j.1399-5448.2010.00698.x PMID: 21518413

[369] Deveault C, Billingsley G, Duncan JL, *et al.* BBS genotype-phenotype assessment of a multiethnic patient cohort calls for a revision of the disease definition. Hum Mutat 2011; 32(6): 610-9.
http://dx.doi.org/10.1002/humu.21480 PMID: 21344540

[370] Feuillan PP, Ng D, Han JC, *et al.* Patients with Bardet-Biedl syndrome have hyperleptinemia suggestive of leptin resistance. J Clin Endocrinol Metab 2011; 96(3): E528-35. http://dx.doi.org/10.1210/jc.2010-2290 PMID: 21209035

[371] Marion V, Stoetzel C, Schlicht D, *et al.* Transient ciliogenesis involving Bardet-Biedl syndrome proteins is a fundamental characteristic of adipogenic differentiation. Proc Natl Acad Sci USA 2009; 106(6): 1820-5. http://dx.doi.org/10.1073/pnas.0812518106 PMID: 19190184

[372] Marion V, Mockel A, De Melo C, *et al.* BBS-induced ciliary defect enhances adipogenesis, causing paradoxical higher-insulin sensitivity, glucose usage, and decreased inflammatory response. Cell Metab 2012; 16(3): 363-77. http://dx.doi.org/10.1016/j.cmet.2012.08.005 PMID: 22958920

[373] Green JS, Parfrey PS, Harnett JD, *et al.* The cardinal manifestations of Bardet-Biedl syndrome, a form of Laurence-Moon-Biedl syndrome. N Engl J Med 1989; 321(15): 1002-9. http://dx.doi.org/10.1056/NEJM198910123211503 PMID: 2779627

[374] Carmi R, Elbedour K, Stone EM, Sheffield VC. Phenotypic differences among patients with Bardet-Biedl syndrome linked to three different chromosome loci. Am J Med Genet 1995; 59(2): 199-203. http://dx.doi.org/10.1002/ajmg.1320590216 PMID: 8588586

[375] Beales PL, Elcioglu N, Woolf AS, Parker D, Flinter FA. New criteria for improved diagnosis of Bardet-Biedl syndrome: Results of a population survey. J Med Genet 1999; 36(6): 437-46. http://dx.doi.org/10.1136/jmg.36.6.437 PMID: 10874630

[376] Iannello S, Bosco P, Cavaleri A, Camuto M, Milazzo P, Belfiore F. A review of the literature of Bardet-Biedl disease and report of three cases associated with metabolic syndrome and diagnosed after the age of fifty. Obes Rev 2002; 3(2): 123-35. http://dx.doi.org/10.1046/j.1467-789X.2002.00055.x PMID: 12120419

[377] Keskin M, Atabek ME, Kurtoğlu S. Bardet-Biedl syndrome with syndrome X: A patient report. J Pediatr Endocrinol Metab 2004; 17(6): 913-5. http://dx.doi.org/10.1515/JPEM.2004.17.6.914 PMID: 15270411

[378] Benzinou M, Walley A, Lobbens S, *et al.* Bardet-Biedl syndrome gene variants are associated with both childhood and adult common obesity in French Caucasians. Diabetes 2006; 55(10): 2876-82. http://dx.doi.org/10.2337/db06-0337 PMID: 17003356

[379] Forsythe E, Beales PL. Bardet–Biedl syndrome. Eur J Hum Genet 2013; 21(1): 8-13. http://dx.doi.org/10.1038/ejhg.2012.115 PMID: 22713813

[380] Lim ET, Liu YP, Chan Y, *et al.* A novel test for recessive contributions to complex diseases implicates Bardet-Biedl syndrome gene BBS10 in idiopathic type 2 diabetes and obesity. Am J Hum Genet 2014; 95(5): 509-20. http://dx.doi.org/10.1016/j.ajhg.2014.09.015 PMID: 25439097

[381] Jeziorny K, Antosik K, Jakiel P, Młynarski W, Borowiec M, Zmysłowska A. Next-Generation Sequencing in the Diagnosis of Patients with Bardet–Biedl Syndrome—New Variants and Relationship with Hyperglycemia and Insulin Resistance. Genes (Basel) 2020; 11(11): 1283. http://dx.doi.org/10.3390/genes11111283 PMID: 33138063

[382] Sherafat-Kazemzadeh R, Ivey L, Kahn SR, *et al.* Hyperphagia among patients with Bardet-Biedl syndrome. Pediatr Obes 2013; 8(5): e64-7. http://dx.doi.org/10.1111/j.2047-6310.2013.00182.x PMID: 23776152

[383] Mujahid S, Hunt KF, Cheah YS, *et al.* The endocrine and metabolic characteristics of a Large Bardet-biedl syndrome clinic population. J Clin Endocrinol Metab 2018; 103(5): 1834-41. http://dx.doi.org/10.1210/jc.2017-01459 PMID: 29409041

[384] Grace C, Beales P, Summerbell C, *et al.* Energy metabolism in Bardet–Biedl syndrome. Int J Obes 2003; 27(11): 1319-24. http://dx.doi.org/10.1038/sj.ijo.0802420 PMID: 14574341

[385] Moore SJ, Green JS, Fan Y, *et al.* Clinical and genetic epidemiology of Bardet-Biedl syndrome in Newfoundland: A 22-year prospective, population-based, cohort study. Am J Med Genet A 2005; 132A(4): 352-60. http://dx.doi.org/10.1002/ajmg.a.30406 PMID: 15637713

[386] Webb MP, Dicks EL, Green JS, *et al.* Autosomal recessive Bardet–Biedl syndrome: First-degree relatives have no predisposition to metabolic and renal disorders. Kidney Int 2009; 76(2): 215-23. http://dx.doi.org/10.1038/ki.2009.116 PMID: 19367329

[387] Imhoff O, Marion V, Stoetzel C, *et al.* Bardet-Biedl Syndrome. Clin J Am Soc Nephrol 2011; 6(1): 22-9. http://dx.doi.org/10.2215/CJN.03320410 PMID: 20876674

[388] Rouskas K, Paletas K, Kalogeridis A, *et al.* Association between BBS6/MKKS gene polymorphisms, obesity and metabolic syndrome in the Greek population. Int J Obes 2008; 32(11): 1618-25. http://dx.doi.org/10.1038/ijo.2008.167 PMID: 18813213

[389] Hendricks AE, Bochukova EG, Marenne G, *et al.* Rare Variant Analysis of Human and Rodent Obesity Genes in Individuals with Severe Childhood Obesity. Sci Rep 2017; 7(1): 4394. http://dx.doi.org/10.1038/s41598-017-03054-8 PMID: 28663568