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Quarterly Medical Review
Lipodystrophy Syndromes

Autoimmunity in lipodystrophy syndromes

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ABSTRACT

Lipodystrophy syndromes are rare, heterogeneous disorders characterized by the complete or partial deficiency of adipose tissue and are classified according to the extent of fat loss in generalized or partial subtypes, or based on the pathogenic mechanisms in genetic or acquired.
While in most cases of congenital forms of lipodystrophy a genetic alteration can be identified, the pathogenic mechanisms responsible for the acquired diseases are not fully clarified.
Based on the evidence of a positive association between most acquired lipodystrophies and autoimmune disorders including immune mediated alterations in the adipose tissue of patients affected by acquired lipodystrophy, a reaction against white adipose tissue antigens is postulated.
Recent acquisitions have shed new light on the possible pathogenic mechanisms and identified novel forms of acquired lipodystrophy which are possibly immune-mediated. The aim of this review is to give an update on acquired lipodystrophies describing pathogenic mechanisms involved and the relationships between acquired lipodystrophies and other autoimmune disorders. Larger studies based on international disease registries are needed to collect accurate information on the prevalence, risk factors, genetic predisposition, natural history, disease markers and treatment efficacy of these ultrarare disorders.

1. Introduction

Lipodystrophy syndromes (LD) are rare and heterogeneous disorders characterized by the complete or partial deficiency of adipose tissue [1].

Lipodystrophies can be classified according to the extent of fat loss in generalized or partial subtypes and, based on the pathogenic mechanisms, in genetic or acquired [2,3].

Especially generalized forms may be associated with the development of metabolic syndrome, caused by the abnormal, ectopic, deposition of fat that cannot be stored in appropriate subcutaneous depots. In this event, surplus calories can only be stored as fat in liver, muscles, pancreas, resulting in insulin resistance, diabetes mellitus, hypertriglyceridemia, and hepatic steatosis or steatohepatitis. Absence or reduction of subcutaneous fat results in a decrease of serum leptin levels that interferes with hunger-satiety signals, leading to hyperphagia, aggravating the metabolic alterations ad thus sustaining a vicious cycle.

While in most cases of congenital forms of lipodystrophy a genetic alteration can be identified, the pathogenic mechanisms responsible for the acquired diseases are not fully clarified.

Based on the evidence of a positive association between acquired lipodystrophies (AL) and autoimmune disorders including immune mediated alterations in the adipose tissue of patients affected by AL, a reaction against white adipose tissue antigens is postulated [1,4].

Some AL have been known since decades but modest advancement on the characterization of pathogenic mechanisms has been made; little is known on the possible genetic contribution, tissue markers and disease progression risk. AL are an important model for improving our knowledge on different aspects of adipose tissue biology. Furthermore, the correct identification of the disease is important because appropriate interventions may change the natural history of it.

The rarity of AL explains for the lack of systematic studies on their pathogenesis. Nevertheless, recent acquisitions have shed new light on the possible pathogenic mechanisms and identified novel forms of AL which are possibly immune-mediated. The aim of this review is to give an update on AL describing pathogenic mechanisms involved and the relationships between AL and other autoimmune disorders. Larger studies based on international disease registries are needed to collect accurate information on the prevalence, pathogenesis, risk factors, genetic predisposition, natural history, disease markers, and treatment efficacy of this ultra-rare disorders [5].

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Table 1
Classification of acquired lipodystrophies.

Acquired Generalized Lipodystrophies	Lawrence Syndrome
	Paraneoplastic
	Immune checkpoint inhibitors-related
Acquired Partial Lipodystrophies	Barraquer-Simons Syndrome
	Hematopoietic-Stem-Cells-Transplant-induced lipodystrophy
	Paraneoplastic
	Immune checkpoint inhibitors-related
Acquired Localized Lipodystrophies	Repetitive trauma/pressure, drug-injections or connective tissue diseases
	Idiopathic

2. Classification and epidemiology

Lipodystrophy syndromes are a group of very rare (estimated prevalence of 3/1.000.000 if excluding HIV-related forms) disorders. From literature searches, the prevalence of LD in Europe has been predicted to be 0.96 and 1.67 cases/million for generalized and partial lipodystrophies, respectively [6]. This estimate is based on very limited number of published articles and on the assumption that 25% of LD cases have been reported in the literature, which is overoptimistic. As a matter of fact, electronic health record information of > 1.3 million adults have recently brought to assess a clinical prevalence of disease, which is higher than previously reported [7]. It is therefore clear that since the disease is under-reported, in the subtle forms never suspected and for the newly described subtypes not calculated yet, the prevalence estimates will be significantly modified in the future. At this time, acquired lipodystrophies subtypes are expected to be less frequent than the corresponding genetic forms (up to 1/10).

Once the diagnosis of lipodystrophy is established, it is mandatory to define whether the disorder is generalized, partial, or localized. In generalized forms, total or near-total loss of subcutaneous fat can be observed over the entire body. In partial forms, fat loss affects large areas, but adipose tissue may accumulate in spared regions, variably distributed, which differ based on the subtype. Localized forms of lipodystrophy are instead limited to restricted body areas. After determining whether the lipodystrophy is generalized or partial, the definition of the specific subtype based on clinical and family history, accompanying disorders and lab tests should be undertaken [3]. The AL classification used in this review is listed in Table 1.

3. Acquired generalized lipodystrophy (Lawrence syndrome)

Acquired generalized lipodystrophy (AGL) is characterized by a nearly complete lack of subcutaneous adipose tissue. The syndrome takes its name from Dr Robert Daniel Lawrence, a British diabetologist, who reported an elaborate description of the disease in 1946 [8].

AGL usually arises during childhood or adolescence but can also manifest in adulthood [9]. Females are affected 3 times more often than males [3]. The loss of subcutaneous fat may initially involve limited sites, for example the arms or legs, but it progresses over a variable amount of time (weeks, months, or, in some cases, years), affecting the entire body, including the palms and soles, in approximately one third and one half of individuals, respectively. Instead, bone marrow, retro-orbital and sometimes intra-abdominal fat is spared. The percentage of total body fat may range between 0.3 and 14.7% [9]. Low plasma leptin levels and a voracious appetite are typically present. [3].

Based on the main clinical characteristics, Misra et al. classified AGL into three subtypes: Type 1, which is preceded by panniculitis; Type 2, which is associated with other autoimmune disorders; Type 3, the idiopathic variety [9]. However, in our opinion this classification should not be viewed in a stringent manner: some Type 1 AGL patients also have clinical evidence of autoimmunity, such as juvenile rheumatoid arthritis, autoimmune hepatitis, Hashimoto's thyroiditis, type 1 diabetes, pernicious anemia, and vitiligo [9,10].

Panniculitis usually appear as inflammatory, swollen reddish subcutaneous nodules sometimes with systemic symptoms such as fever, arthralgia, and malaise. Biopsies of the panniculitis nodules have revealed infiltration of lymphocytes and histiocytes in subcutaneous fat with a granulomatous reaction and multinuclear giant cells. Areas of localized lipoatrophy follow the area where panniculitis develops, progressing over time into a generalized fat loss. Differential diagnosis should be posed with an auto-inflammatory, genetically determined disease causing lipomuscular atrophy and joint contractures, microcytic anemia, and panniculitis-induced lipodystrophy (Nakajo-Nishimura syndrome). Additional characteristics of the latter disease include intermittent fever, hyper-gammaglobulinemia, hepatosplenomegaly, and calcification of the basal ganglia [11]. According to Misra A et al., Type 1 AGL patients exhibit less frequently metabolic alterations (44% diabetes and 59% hypertriglyceridemia) compared to other varieties of AGL [9], probably reflecting the less extensive fat loss, a slower disease progression, or a more recent disease development.

Type 2 AGL patients are identified as those who display autoimmune diseases without panniculitis preceding the loss of subcutaneous fat but, as reported above, Type 1 AGL patients may present associated autoimmunity: it is therefore possible that no real distinction exist between the 2 groups and no dissimilar pathogenic mechanisms are in place.

Type 3 AGL is supposed to be the most common variety; by definition, there is no onset with panniculitis nor sign of accompanying autoimmune disorders and the mechanisms involved are poorly understood (hence defined as "idiopathic"), in some cases possibly genetically driven. In our view, since many AGL patients are not systematically screened for autoimmunity, it is difficult to define the real prevalence of this "subtype".

The autoimmune diseases associated with AGL include both organ-specific and systemic autoimmune diseases such as autoimmune thrombocytopenia [9,12], autoimmune hepatitis [9,13,14], juvenile dermatomyositis [9,14], Grave's disease [14], Hashimoto thyroiditis [9], Sjogren syndrome [9], rheumatoid arthritis [9], autoimmune hemolytic anemia [9], Crohn's disease [15], type 1 diabetes [16,17], autoimmune polyglandular syndrome type 1 [18], common variable immunodeficiency [19], and chronic urticaria and angioedema [9,14].

The extremely rare simultaneous occurrence of generalized lipodystrophy and type 1 diabetes mellitus leads to a mixed phenotype characterized by insulin resistance and insulinopenia, making more challenging the correct diagnosis and, therefore, the achievement of a good glycemic control [16,17].

AGL patients have been reported to display the presence of multiple organ-specific and non-organ-specific autoantibodies which are listed in Table 2. From the small cohorts so far published in the literature, it is difficult to establish if and which auto-antibodies are more frequent in AGL patients. Furthermore, sometimes the positive testing is not associated with overt disease [9,13,14]. In our opinion, a wide autoimmune screening should be encouraged for both informative and preventive purposes and, in the event a subclinical disease is present, a strict follow up is required to verify if it becomes clinically manifest over time. Table 3

Three patients with AGL have been reported to have autoimmune hepatitis and low serum C4 levels [20], a component of the "classical" complement pathway. 'Classical' and 'alternative' complement pathways are triggered differently, but both activate specific C3 convertases that lead to complement membrane attack complex production, disrupting the cell membrane of target cells. Therefore, incongruous complement activation may be responsible for autoimmune diseases [21].

Table 2
Summary of main characteristics of acquired generalized lipodystrophy (Lawrence Syndrome).

F:M prevalence	3:1
Age of onset	Childhood or adolescence
Fat loss distribution	Generalized (sometimes palms and soles) Preserved retro-orbital and bone marrow fat
Percentage of body fat	< 15%
Onset of disease	Panniculitis (25%) Autoimmune diseases
Laboratory tests	Ab anti-perilipin positive in 60% of patients* Reduced C4 levels (rare, associated with autoimmune hepatitis)
Associated autoimmune diseases reported to be associated**	Autoimmune thrombocytopenia, autoimmune hepatitis, juvenile dermatomyositis, Graves' disease, Hashimoto's thyroiditis, Sjogren syndrome, rheumatoid arthritis, autoimmune hemolytic anemia, Crohn's disease, type 1 diabetes, autoimmune polyglandular syndrome type 1, common variable immunodeficiency, chronic urticaria and angioedema
Other	Increased risk of lymphoma (7%)

*experimental.
** if AGL is confirmed it may be helpful testing for: TgAb, Antithyroglobulin; TPOAb, anti-thyroid peroxidase; APCA, anti-gastric parietal cells, 21OHAb, anti 21-hydroxylase; IgA/IgG-tTG, anti-transglutaminase; EMA, anti-endomysium; GAD65Ab, anti-glutamic acid decarboxylase; ANA, anti-nuclear antibodies; ENA, anti-extractable nuclear antigens; anti-native dsDNA; ANCA, antineutrophil cytoplasmic; RF, immunoglobulin M rheumatoid factors; ACA, anti-cardiolipin antibodies; LKM, anti-liver-kidney microsome; ASMA, anti-smooth muscle; AMA, anti-mitochondrial antibodies-AMA; LA, lupus anticoagulant; DAT/IAT, direct/indirect antiglobulin test.

Table 3
Summary of main characteristics of acquired partial lipodystrophy with cephalocaudal progression (Barraquer-Simons Syndrome).

F:M prevalence	4:1
Age of onset	Childhood or adolescence (mean age 7–8 yrs)
Fat loss distribution	Cephalocaudal pattern of subcutaneous fat loss (face, shoulder girdle, upper extremities, and trunk); normal breast development, frequently excess fat accumulation in the lower body parts (gluteal regions, legs)
HLA	Possible association with HLA-DRB1×11 allele (in particular*11:03)
Laboratory tests	Reduced C3 (50–80%) IgG "Nefritic Factor" (70%) Organ and/or non-organ autoantibodies (60%) Anti-C3 auto-antibodies (38.5%) Anti-P and anti-FB auto-antibodies (31%)
Prevalence of autoimmune diseases	Around 40%
Associated autoimmune diseases reported to be associated	Systemic lupus erythematosus, dermatomyositis, autoimmune thyroiditis, localized scleroderma, idiopathic thrombocytopenic purpura, Sjögren's syndrome, vitiligo, rheumatoid arthritis
Other	30–40% membranoproliferative glomerulonephritis

Based on the evidence of a frequent association between acquired lipodystrophy and autoimmune disorders, an autoimmune destruction of adipocytes is strongly suspected, although the target antigen (s) has not been established [1,4].

Hubler et al. were the first to demonstrate the presence of autoantibodies (IgG deposits) against adipocyte membranes, by using direct immunofluorescence in a subcutaneous biopsy of a patient with AGL [22]. Nevertheless, they were not able to identify the specific antigen (s). Afterwards, by using skin biopsy samples from a patient with AGL, another research group demonstrated that the loss of adipose tissue was caused by apoptosis of adipocytes mediated by the CD95 system [23]. More recently, Corvillo et al. showed the presence of autoantibodies against perilipin-1 in 60% (3/5) of patients with AGL [24].

From what has been described so far, it is likely that immune reactions against adipose tissue auto-antigens play a key role in AGL. Among the potential tissue specific auto-antibodies that might be discovered, it will be essential to establish if they represent only an epiphenomenon of the autoimmune aggression or if they also exhibit a pathogenic role. Importantly, chronic over-activation of the immune system in AGL patients increases the risk of developing lymphomas, in particular peripheral T-cell lymphomas, with a prevalence of approximately 7% in this specific subtype [25].

4. Acquired partial lipodystrophies

For a long time, acquired partial lipodystrophies has been a synonym of Barraquer-Simons syndrome, a very puzzling disease usually developing during childhood and adolescence, and characterized by very precise site-specific lipoatrophy. Lately, other forms of acquired partial lipodystrophy have been described and added to the classification list. The most frequent form of acquired lipodystrophy is the one which is secondary to combined anti-retroviral HIV pharmacological treatments. These drugs affect the health of adipose tissue by different mechanisms: mitochondrial toxicity, local inflammation, perturbation of adipocyte differentiation or impaired signal transduction or hormonal production [26]. Since this form is usually managed by infectious disease specialists, we will not discuss this subtype in the current review.

Lipodystrophy may also develop after complex treatment related to bone marrow transplant occurring during childhood [27]. Finally, even rarer forms of paraneoplastic [28] and iatrogenic [29] AL have been described. Needless to say that the disease mechanisms are very different and in most cases probably involve autoimmunity. Since acquired partial lipodystrophies (APL) are less likely to impact metabolism, it is reasonable to hypothesize that a majority of them may be never recognized.

4.1. Acquired partial lipodystrophy with cephalocaudal progression (Barraquer-Simons syndrome)

Barraquer-Simons syndrome (BS) is a very rare APL characterized by a cephalocaudal loss of subcutaneous adipose tissue. The first physician who described the disease was Dr Silas Weir Mitchell, an American neurologist, in 1885 [30] but the name of the syndrome derives from Dr Louis Barraquer, a Spanish neurologist who described

a young woman who had face fat atrophy after a flu at age of 13 years, and Arthur Simons, a German neurologist who widened the knowledge on what he called a "progressive cephalothoracic lipodystrophy" [31,32].

BS is more common in women than men (F:M; 4:1) and fat loss usually begins in late childhood or adolescence, rarely up to the 4th decade of life. Patients usually do not have family history of lipodystrophy. Fat loss initially affects the face and progresses to the shoulder girdle, upper extremities, and trunk (sparing breasts) in a process that can last weeks, months, or years. Quite frequently, excess fat accumulation in the lower body parts such as lower abdomen, gluteal regions and legs is observed, suggesting an attempt at compensation. Several autoimmune diseases, in particular systemic lupus erythematosus and dermatomyositis, less frequently autoimmune thyroiditis, localized scleroderma, idiopathic thrombocytopenic purpura and Sjögren's syndrome, vitiligo and rheumatoid arthritis have been reported to be associated with BS [33–35]. Recent findings suggest the prevalence of autoimmune diseases to be around 40%, the majority of patients (61.5%) being positive for at least one of the autoantibodies usually tested when screening for autoimmunity: antinuclear, ENA (extractable nuclear antigen) panel tests, which search for autoantibodies to proteins in the cell nucleus, anti-cardiolipin, anti-parietal cells, glutamic acid decarboxylase, anti-thyroglobulin, anti-thyroid peroxidase, direct anti-globulin test, rheumatoid [35].

Furthermore, it is known from the 70′ [36] that the majority (up to 80%) of patients show low serum C3 complement. This feature is indeed widely established as a bio-marker recommended for the differential diagnosis of BS [1]. Serum concentrations of the classical component pathways (C1q, C2, C4) are within the normal range, suggesting C3 activation via alternative pathway. C3 nephritic factor auto-antibody (C3NF), a pool of polyclonal immunoglobulin G, stabilizes the enzymatic complex C3 convertase, thus over-activating the alternative pathway of the complement system [21]. As a consequence, patients who display the presence of serum C3NF also have reduced C3 levels [37]. C3NeF was the most frequently found autoantibody (70%), followed by anti-C3 (38.5%), anti-P and anti-FB (31%) [35]. Possible disease mechanisms linking C3 hypocomplementemia, activation of the alternative pathway of the complement and the site specific reduction of subcutaneous tissue remain to be established. An interesting finding is that C3NeF has the ability to lyse the adipocytes [38]; furthermore, complement system over-activation occurs within the adipose tissue, as proven by local detection of IgG, C3, C5a and C5b-9 complement-directed injury [39]. Remarkably, complement factor D (FD), also known as adipsin, a serine protease involved in the activation of the alternative pathway of the complement system, is secreted by several cell types, with mature adipocytes and macrophages being the principal source in human [40]. Elevated concentrations of FD in BS sera have been recently found; increased FD staining was also detected in the stroma-vascular cells and in adipocytes (cytoplasmic staining) of a patient's partially atrophic adipose tissue [37]. Hopefully, FD may become an additional clinical biomarker to be used in the diagnosis and prognosis of BS patients.

Following the onset of lipodystrophy, some (approximately 20–40%) but not all C3NF positive patients develop membranoproliferative glomerulonephritis [36]. All the above mentioned elements, taken together, suggest an autoimmune pathogenesis for BS, similarly to AGL.

Infections have been proposed as environmental triggers for the induction of autoimmunity. Several investigators have identified infections frequently preceding the onset of BS, especially measles [33,36], varicella, rubella, mumps and meningitis [41,42] but the precise role of viral infections in the pathogenesis of the disease is not clear.

Human Leukocyte Antigens (HLA) status has been investigated in 13 affected patients in order to identify a possible association between HLA genetic variants and the disease: allele DRB1×11 was present in 54% of BS patients, and the majority of them (31%) were positive for *11:03, a prevalence higher than in the general population [35].

BS presents usually milder metabolic derangement when compared to generalized or familiar lipodystrophies, but a relevant portion of patients may display at least one metabolic abnormality at time of evaluation [43].

4.2. Acquired partial lipodystrophy associated with total body irradiation and hematopoietic stem cell transplant

Cancer patients treated in childhood with hematopoietic stem cell transplant (HSCT) have a higher incidence of insulin resistance, glucose intolerance and body fat redistribution, characterized by increased central to peripheral adiposity, reduced subcutaneous and increased visceral fat towards higher visceral fat depots, resembling a partial lipodystrophic phenotype [44–48].

Within the last 15 years, several patients who developed partial LD after HSCT in early life were described [for a summary see 48,49]. A novel subtype of APL developing after complex treatment related to bone marrow transplant occurring during childhood has been then proposed [27,50]. It is common opinion that HSCT-induced lipodystrophy may frequently pass unrecognized.

All these cases have in common fat loss at the extremities and gluteal region with lipo-hypertrophy of subcutaneous fat in the face and neck and young age at the time of HSCT.

The major prerequisite for the development of the disease seems to be a damaging effect of total body irradiation on adipose tissue. Pharmacologic treatment during conditioning and graft-versus-host disease (GVHD) may contribute to the development of the disease. Cytotoxic treatments or GVHD by taking place during a very sensitive window of time for the commitment of adipose stem cells, may affect the normal development of fat mass causing, on average 10 years later, partial lipodystrophy. The involvement of B-cell response and autoantibodies in chronic GVHD are reminiscent of an autoimmune disease [51]. Interestingly, APL and metabolic disturbances have been recently observed also in two adults after bone marrow or liver transplantation associated with development of GVHD [52]. Therefore, although at time of this writing there is no evidence for a pure autoimmune mechanism causing this specific subtype of LD, since GVHD may be involved, we found appropriate the reference to this LD in the current review.

5. Checkpoint inhibitors induced lipodystrophy

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies used to treat advanced solid cancers. By blocking the surface receptors involved in immune regulation, such as the programmed cell death protein-1 (PD-1), the programmed cell death protein ligand 1 (PDL-1) and the cytotoxic T-lymphocyte antigen 4 (CTLA-4), ICIs activate the immune system against cancer cells, thus altering the cancer cell's ability to avoid immune-cell recognition [53]. As a result, ICIs boost a strong anticancer reaction but, at the same time, can prompt immunologically-mediated toxic effects known as immune-related adverse events (irAEs) and among them, the development of autoimmune diseases. IrAEs involve gastrointestinal tract, endocrine glands, skin and liver [54]. Acquired partial or generalized lipodystrophy has been so far reported in five cases treated with ICIs [29,55–58]. Patients were mostly females (F:*M* = 4:1), with a mean age of 53.4 years (range 34–67). All reported cases were associated with anti-PD1 monoclonal antibodies (3 with nivolumab and 2 with pembrolizumab) used to treat advanced melanoma (4/5 cases) or renal cell carcinoma (1/5).

All patients are described as having a rapidly progressing pattern of fat loss, and 3 of them may be partial forms, given their physical appearance, serum leptin values and the reported percentage of body fat [29,56,57]. Patients started losing subcutaneous adipose tissue

after a variable period of time (mean 7 months, range 2−18 months). After the onset of lipodystrophy, patients developed metabolic complications such as diabetes, hypertriglyceridemia and/or hepatic steatosis. Subcutaneous fat biopsies revealed a disorganization of fat lobules with chronic infiltration of T cells and, in 3 out of 5 patients, clinical signs of panniculitis. Although the mechanism of fat loss in these patients is not clearly elucidated, immune checkpoint inhibitors may disrupt immunological tolerance of T cells against adipocyte antigens.

For this reason, acquired partial and generalized lipodystrophy should be included in the list of autoimmune endocrine adverse events associated with ICIs treatment, and therefore suspected when patients show an unusual fat loss, episodes of panniculitis, development or worsening of pre-existing metabolic complications.

6. Paraneoplastic acquired lipodystrophy

AL have also been described as a paraneoplastic manifestation of brain tumors in infants and young children. To date, 5 cases have been reported: 3 cases of AL in patients with pilocytic astrocytoma, the most common low-grade pediatric central nervous system tumor [28], one with hypothalamic pilomyxoid astrocytoma [59], and the fifth with craniopharyngioma [60]. Four out of the 5 patients showed a generalized pattern of fat loss [28,59], while the one with craniopharyngioma displayed increased subcutaneous fat in the face and neck, protuberant abdomen, buffalo hump and lipoatrophic limbs [60].

Almost all patients are described as having at least one metabolic abnormality. In these patients, acquired lipodystrophy stigmata and metabolic comorbidities reversed or improved after tumor surgical resection and radiation or chemotherapy, which supports the hypothesis that acquired lipodystrophy may develop as a paraneoplastic manifestation: neoplasms could generate autoantibodies against adipocytes or other substances that stimulate excessive lipolysis, resulting in (potentially reversible) subcutaneous fat loss [28].

Screening for brain tumors should be considered in infant or young children with unexplained loss of subcutaneous adipose tissue suggestive of lipodystrophy.

7. Acquired localized lipodystrophy

Acquired localized lipodystrophies are characterized by a selective loss of subcutaneous fat from restricted regions of the body. The local disappearance of subcutaneous fat can be in one or more areas of the limbs, trunk and/or face, and it is usually asymmetrical. Given the preservation of most subcutaneous adipose tissue, acquired localized lipodystrophies are not associated with metabolic abnormalities [61]. Localized lipodystrophy can be idiopathic when appearing without triggering factors. The diagnosis of localized lipodystrophy is clinical, although a biopsy and histological examination is required in some cases to rule out underlying diseases. Soft tissues ultrasound can be a useful diagnostic tool; it allows safe and quick identification of a localized loss of subcutaneous adipose tissue compared to the surrounding areas.

Localized lipoatrophy is sometimes secondary to repeated mechanical trauma/pressure, likely related to a reduced vascular perfusion caused by the repeated trauma on the same area [61]. Drug-induced localized lipodystrophy has been reported after subcutaneous, intramuscular and dermal injections of insulin, corticosteroids, antibiotics (amikacin, penicillin, gentamicin), methotrexate and vaccines (influenza, papillomavirus and Diphtheria Pertussis Tetanus-DPT) [62−68]. The triggering mechanism, in this case, is probably drug-specific. The most common form is insulin-induced localized lipoatrophy [3]. With the recent introduction of highly purified human insulins and their analogs, lipoatrophy incidence has decreased. The repeated injection at the same site could lead to a local subcutaneous adipose tissue trauma [69], a local immune reaction to insulin crystals, which may lead to a local hyperproduction of TNFα and IL-6 constraining adipocyte differentiation and adipogenesis [70]. Increased lipolysis caused by chronic exposure to high local insulin concentrations and thus triggering severe insulin resistance may contribute to development of the lesion [71].

High titers of anti-insulin antibodies have been detected [69] but they have no diagnostic role. Lipoatrophic areas can compromise insulin absorption, leading to greater glycemic variability.

Acquired localized lipodystrophies have also been reported to be associated with connective tissue diseases: lupus erythematosus, morphea, dermatomyositis or panniculitis. Some of these patients may be positive for antinuclear antibodies (ANA) or anti dsDNA antibodies [61]. To date, no specific, long-term effective treatment exists for localized lipodystrophy. Insulin-injection lipoatrophies have been treated with intralesional steroids with good results [72], but there is lack of trials in this regard. Therefore caution should be recommended in their use, especially if we take into account that corticosteroid injections themselves are reported to cause lipoatrophy.

8. Treatments

At this time there is no evidence of treatments capable of modifying the progression of fat loss in acquired lipodystrophies. Corticosteroids have been occasionally used together with immunosuppressive drugs but the efficacy of this approach is limited, with the possible exception of steroidal treatments in the event of panniculitis associated with severe local inflammation and pain. For the above mentioned reasons, corticosteroids and immunosuppressive drugs have no indication in the context of acquired lipodystrophies [1].

Substitutive recombinant leptin (metreleptin) treatment is approved by the European Medicines Agency for the treatment of patients with AGL or BS with significant metabolic derangements not responsive to standard therapies. Treatment with metreleptin is usually well tolerated and improves metabolic complications, hyperphagia, quality of life and, likely, survival [1,73,74]. Since leptin has pleiotropic immunomodulatory activities, concern was raised whether the substitutive treatment might accelerate or favor autoimmunity in subjects with AL. Field experience showed that metreleptin did not alter the clinical course of autoimmune disease nor the clinical efficacy of immunosuppressive treatments prescribed for the associated autoimmune diseases [14]. Metreleptin is also useful for the treatment of metabolic disturbances in HSCT-associated LD [52,75].

Risks of development of neutralizing-metreleptin-activity-antibodies (NMAA) are unclear and should be weighed alongside the benefits of therapy [76]. At this time there is no report suggesting a higher risk for development of NMAA in AL. Higher risk for lymphoma development has instead been reported in patients with AGL, both in the absence and presence of metreleptin treatment [25]. The increased risk of malignancy in these individuals may be attributable to the chronic autoimmune disease; however, a role of metreleptin in cancer growth cannot be ruled out [25].

Body shape changes, due to abnormal distribution of adipose tissue are stressful and worrisome because they have a relevant impact on physical appearance [77]. Experience regarding cosmetic surgery is very limited but autologous fat transfer, dermal fillers, prosthetic insertions, or muscle grafts have been used [1]; an increasing demand from patients and consequently solid research evidence in this regard are expected in the years to come.

Author contributions

G.C., S.M. and F.S. conceived and wrote the manuscript. C.P., D.G., revised the manuscript. All authors have read and agreed to the published version of the manuscript.

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