Early Access
Review

Veins and Lymphatics

eISSN 2279-7483
https://www.pagepressjournals.org/index.php/vl/index

Veins and Lymphatics 2026 [online ahead of print]

To cite this article:
Vainberg D, Kaftalli J, Ferrari L, et al. From rare familial mutations to multifactorial disease: aldo-keto reductase 1C enzymes as a central biological pathway in lipedema. Veins and Lymphatics 2026;15:15495.
doi:10.4081/vl.2026.15495

From rare familial mutations to multifactorial disease: aldo-keto reductase 1C enzymes as a central biological pathway in lipedema

Daniil Vainberg,[1] Jurgen Kaftalli,[2] Luca Ferrari,[2] Kristjana Dhuli,[2] Beatrice Della Frera,[2] Dominika Veselenyiova,[1] Ahmad Jainul Abidin,[3] Serena Michelni,[4] Silvia Michelni,[5] Sandro Michelni,[6,7] Matteo Bertelli[2,3,8]

[1]Department of Biology, Institute of Biology and Biotechnology, Faculty of Natural Sciences, University of SS. Cyril and Methodius, Trnava, Slovakia;

[2]MAGI'S LAB, Rovereto (TN), Italy;

[3]MAGI EUREGIO, Bolzano, Italy;

[4]Unit of Physical Medicine, "Sapienza" University of Rome, Italy;

[5]Unit of Neurosurgery, University of "Tor Vergata", Rome, Italy;

[6]Vascular Diagnostics and Rehabilitation Service, San Giuseppe Hospital, Marino (RM), Italy;

[7]Ospedale San Giovanni Battista (ACISMOM), Rome, Italy;

[8]MAGISNAT, Atlanta Tech Park, Peachtree Corners, USA;

Abstract

The discovery of pathogenic variants in *AKR1C1* and *AKR1C2* in ultra-rare familial lipedema highlights steroid hormone metabolism as a core mechanism affecting about 11% of women during reproductive age. Lipedema represents a complex disease shaped by the interplay between rare mutations, common regulatory variants, and environmental exposures. This review outlines how

ultra-rare monogenic mutations can illuminate the genetic and environmental bases of multifactorial lipedema.

A systematic literature review (2000-2025) was performed using PubMed, Web of Science, and Google Scholar. Studies were identified with MeSH and keyword searches including lipedema, *AKR1C1*, *AKR1C2*, steroid metabolism, adipose tissue, obesogens, epigenetics, polycyclic aromatic hydrocarbons, endocrine disrupting chemicals, air pollution, and dietary hormones.

The *AKR1C1* p.Leu213Gln loss-of-function variant decreases progesterone inactivation by ~50% due to catalytic domain destabilization, leading to local progesterone accumulation. *AKR1C2* gain-of-function variants and overexpression, found in 24% of cases, enhance DHT inactivation, converting it to 3α-androstanediol and suppressing anti-adipogenic androgen signaling. Population screening revealed three *AKR1C1* polymorphisms associated with increased lipedema risk. The *AKR1C2* regulatory variant rs28571848 in a glucocorticoid receptor site elevates *AKR1C2/AKR1C3* expression and trunk fat mass independently of BMI. Environmental agents such as polycyclic aromatic hydrocarbons activate *AKR1C1* via Nrf2-ARE signaling (3-10-fold induction), while steroid hormones promote adipocyte differentiation.

Lipedema arises from an interaction between genetic susceptibility and environmental factors. Understanding the *AKR1C* pathway clarifies how genetic variants and obesogens disrupt steroid metabolism and induce epigenetic reprogramming, leading to clinical manifestations.

Key words: lipedema, *AKR1C1, AKR1C2*, steroid metabolism, obesogens.

Correspondence: Luca Ferrari, MAGI'S LAB, via Maioliche 57, 38068 Rovereto (TN), Italy.

E-mail: luca.ferrari@assomagi.org

Introduction

Lipedema remained a clinical enigma for eight decades despite affecting an estimated 11% of women during reproductive life, with no identified causative genes and no understanding of molecular pathogenesis.[1] The disease exhibits striking familial clustering because about 50% of cases show positive family history while the disease follows autosomal dominant inheritance patterns.[2] The first genetic cause of the disease was discovered through the identification of the *AKR1C1 p.Leu213Gln* mutation which segregates with lipedema across three generations.[3] The research which followed identified *AKR1C2* mutations and their overexpression patterns through the work of Kaftalli, Bertelli, and their colleagues.[3] These findings suggest that lipedema may represent a metabolic disorder involving altered steroid hormone processing within subcutaneous fat tissue.[4,5]

The clinical presentation of lipedema shows unique characteristics which medical professionals often fail to recognize.[1] Affected individuals show symmetrical bilateral expansion of their limbs which does not respond to their efforts of dietary control and weight loss and physical activity.[6] The lipedema condition leads to adipocyte cells which grow larger and increase in size.[7] Lipedema is typically resistant to caloric restriction, weight loss, and physical exercise, although lifestyle interventions remain important.[8, 9] The lipedema condition causes adipose tissue to develop into a distinct medical condition which manifests through the presence of tender and nodular body fat that exhibits abnormal physical characteristics including easy bruising and hypersensitivity to pressure.[10,11] The disease follows a relentless progressive course, staging from localized involvement to bulky extrusions of skin and fat that can severely restrict mobility, and may ultimately be complicated by secondary lymphedema - a condition termed lipo-lymphedema.[1]

The hormonal link to lipedema has long been recognized. The condition typically appears during puberty, the third decade of life, or after menopause or childbirth periods of major estrogen shifts. It affects women almost exclusively, with rare male cases linked to disorders causing high estrogen and low androgen levels. Although this hormonal pattern is well known, the molecular pathway connecting sex hormones to pathological fat development remains unclear, limiting targeted treatments.[12]

The genetic link to lipedema first became evident through research about how the condition runs in families. The research found that 50% of patients have a positive family history while affected families showed autosomal dominant inheritance patterns.[13] The genetic studies used candidate gene methods and traditional linkage analysis methods to find causative variants, but they failed to identify any thus resulting in lipedema being classified as an undiagnosed condition. The diagnostic deadlock started to change when next-generation sequencing technologies were used to study familial lipedema patient groups.[14]

The medical genetics principle states that single families contain rare mutations which show strong penetration because these mutations create biological pathways which lead to common multifactorial diseases when they experience slight disruptions from frequent genetic variants and environmental factors.[15] This framework proposes a complete explanation for lipedema development which results from three linked systems: (i) genetic factors because they include both extremely rare coding mutations with major impacts and typical regulatory polymorphisms with minor impacts;[16] (ii) environmental factors which may create long-lasting changes to *AKR1C* gene expression through environmental exposure; [5] and (iii) environmental amplification which may activate *AKR1C* expression while altering steroid production and promoting fat storage in subcutaneous tissue.[17] The mechanisms lead to two outcomes which decrease androgen

bioavailability and increase estrogen-progesterone signaling within subcutaneous adipose tissue. This could create a pro-adipogenic hormonal microenvironment which promotes adipose tissue growth and may result in excessive fat accumulation.[18]

Materials and Methods

A systematic literature review was conducted which retrieved data from multiple electronic databases such as PubMed, Web of Science, and Google Scholar between the years 2000 and 2025. Several MeSH and keyword search terms were integrated to identify relevant literature comprehending the role of *AKR1C* enzymes as central biological pathway in pathogenesis of lipedema. The search terms include lipedema AND (*AKR1C1* OR *AKR1C2*); steroid metabolism AND adipose tissue; obesogens AND obesity; polycyclic aromatic hydrocarbons AND *AKR1C*; (phthalates OR bisphenol A) AND steroid metabolism; hormones in beef; epigenetics AND *AKR1C*. The literature search was finalized in February 2026, and studies were screened by the authors based on predefined inclusion criteria. Studies were selected based on the following criteria: (i) original research articles, reviews, or clinical trials examining *AKR1C* enzymes in steroid metabolism or adipose tissue; (ii) studies investigating environmental obesogens and their effects on steroid metabolism or adipogenesis; (iii) genetic studies identifying mutations or polymorphisms in *AKR1C* genes; (iv) mechanistic studies elucidating molecular pathways relevant to lipedema pathogenesis. Exclusion criteria included: (i) studies not available in English; (ii) studies without clear methodology or results; (iii) duplicate publications.

Evidence was evaluated and weighted based on (i) study design (randomized controlled trials and mechanistic studies weighted higher than observational studies); (ii) sample size and statistical power; (iii) relevance to human lipedema pathophysiology (human studies weighted higher than

animal or *in vitro* models); (iv) consistency across multiple independent studies; (5) biological plausibility and mechanistic coherence with the *AKR1C* pathway hypothesis. The evidence synthesis used a weight-of-evidence method which combined molecular genetics with enzymology, steroidomics, environmental toxicology, and epigenomics.

Results

Molecular basis of lipedema pathogenesis: steroidomics analysis of AKR1C *enzymes*

The *AKR1C* subfamily encompasses four enzymes which exhibit high sequence similarity because their protein sequences maintain 84% identity whereas they function as NAD(P)H-dependent oxidoreductases which perform reductions at three steroid nucleus C3, C17, and C20 positions.[15,19] The enzymes demonstrate high functional flexibility because they function between three different steroid reductase activities which allow them to manage various active ligand levels that bind to androgen and estrogen and progesterone receptors through their prereceptor control mechanism.[18] *AKR1C1* (20α-hydroxysteroid dehydrogenase) functions mainly to convert progesterone into its inactive form through its NADPH-dependent reduction pathway which results in 20α-hydroxyprogesterone production while also reducing 5α-Dihydrotestosterone (DHT) to 3β-androstanediol, an estrogen receptor β agonist. *AKR1C2* (type 3 3α-hydroxysteroid dehydrogenase) performs DHT reduction to 3α-androstanediol which acts as a weak androgen receptor agonist that binds with ten times less affinity than the most potent endogenous androgen.[5,15]

Understanding tissue distribution of *AKR1C* enzymes provides essential information to study how lipedema develops. Blouin *et al*. found that both *AKR1C1, AKR1C2,* and *AKR1C3* showed activity in subcutaneous and omental adipose tissue from men and women, with subcutaneous depot

exhibiting higher activity than other sites.[20] The study found that *AKR1C* enzyme mRNAs showed higher levels of expression than all other steroid-converting enzymes. The study showed that mature adipocytes showed a higher DHT inactivation rate than preadipocytes (755±830 *versus* 245±151 fmol 3α/β-diol per μg protein over 24 hours), while adipocyte differentiation resulted in *AKR1C* enzyme expression and activity, which created a feed-forward system that started with adipogenesis to increase *AKR1C* expression which reduced DHT levels to drive more adipocyte differentiation.[21]

The depot-specificity is striking: subcutaneous 5α-DHT inactivation was significantly higher than omental fat, creating greater capacity for androgen inactivation in subcutaneous depots which may contribute to preferential subcutaneous fat accumulation in lipedema.[21] The process of 5α-androstan-3α,17β-diol formation showed significant stimulation through dexamethasone treatment in preadipocytes, which showed complete inhibition after RU486 treatment, suggesting that glucocorticoid receptor activation promotes androgen inactivation.[22] These findings indicate that *AKR1C* enzymes showed increased activity in mature adipocytes, which supported their role in subcutaneous adipose tissue deposition, while their activity also led to increased adipogenic processes, which resulted in more subcutaneous fat development.[23]

Ultra-rare familial mutations lead to genetic disorders

The *AKR1C1 p.Leu213Gln* (L213Q) variant which Michelini and his colleagues discovered provides the first strong evidence implicating steroid metabolism as a key mechanism in lipedema development.[14] The *L213Q* substitution occurs at a highly conserved residue within the catalytic domain which leucine 213 contributes to the hydrophobic core surrounding the substrate binding pocket and active site architecture. The molecular dynamics simulations showed that when

nonpolar leucine got replaced by polar glutamine the hydrophobic environment became unstable because hydrogen bonds between NADP and the enzyme broke down which resulted in a 50% reduction of both substrate binding and catalytic efficiency.[3]

This partial function loss may lead to tissue-specific progesterone accumulation which could occur in subcutaneous adipose tissue where progesterone accumulation may promote adipocyte differentiation and lipid storage through well-established adipogenic pathways.[3,23,24]

Kaftalli, Bertelli, and colleagues used molecular dynamics simulations to study how *AKR1C1* genetic variants which cause lipedema affect their biological functions.[19] The three genetic variants which researchers discovered in lipedema patients showed that they disrupted *AKR1C1* protein functions. Computational methods used gnomAD population database to discover eight *AKR1C1* polymorphisms which researchers used structural modeling and information theory analysis to establish as potential predisposing factors for lipedema development.[4] This research suggests that a single gene contains both uncommon genetic variations that produce significant effects and typical genetic variations which result in minor effects, thus establishing a genetic pathway from monogenic familial lipedema to polygenic population susceptibility.

AKR1C2 was discovered by Michelini and colleagues, which established activating mutations as well as 24% of patients who had overexpression without any coding variants.[14] A deletion mutation was presented that affects the *AKR1C2* C-terminal region and results in increased enzyme activity through the *Ser320PheTer2* mutation. *AKR1C2* was found to be overexpressed in 5 of the 21 lipedema patients tested who did not carry *AKR1C2* gene mutations according to qPCR results. [14]

DHT acts as a potent anti-adipogenic signal, and its inactivation may favor adipocyte differentiation.[22] Increased *AKR1C2* function may reduce anti-adipogenic signaling by transforming DHT into 3α-androstanediol which then blocks local DHT distribution throughout

the body. The research team confirmed through experimental studies that the siRNA-based reduction of *AKR1C2* produced a significant decline in both normal and glucocorticoid-driven androgen metabolism rates ($p<0.05$) while *AKR1C2* knockdown enhanced DHT's ability to stop preadipocyte development and it also caused a decline in lipid buildup and G3PDH activity and FABP4 mRNA production in preadipocytes that developed after DHT exposure.[22]

Common regulatory polymorphisms: population susceptibility

The discovery that 24% of lipedema patients show *AKR1C2* overexpression without any coding mutations led researchers to examine regulatory variants which explain how lipedema develops through common pathways that bypass rare coding mutations.[5] Genetic variants in *AKR1C* genes associated with lipedema are summarized in Table 1. The research conducted by Ostinelli *et al*. discovered two SNPs which exhibit strong functional impact: rs28571848 which belongs to a Glucocorticoid Receptor (GR) binding site and *rs34477787* which functions as a retinoid acid-Related Orphan Receptor Alpha (RORα) binding site.[25]

Using RNA sequencing data from severely obese patients and 856 women to demonstrate that *AKR1C2* and *AKR1C3* expression in subcutaneous adipose tissue showed significant positive correlation with trunk fat mass percentage in women while the expression levels were highest in mature adipocytes and adipocyte-committed progenitor cells.[25] The r*s28571848* SNP affected *AKR1C3* expression in both subcutaneous and visceral adipose tissue in women, with carriers exhibiting increased visceral adipose tissue *AKR1C* activity compared to wild-type genotype.[25,27]

The researchers established the mechanistic link between glucocorticoids and *AKR1C2* by conducting experiments which demonstrated that cortisol production in whole adipose tissue samples showed a positive relationship with androgen inactivation in both subcutaneous and

omental adipose tissue (p=0.05).[22] The research found that men showed higher DHT inactivation through dexamethasone (1 μM) stimulation in omental fat tissues compared to subcutaneous fat tissues which resulted in a positive relationship between BMI and DHT inactivation rates induced by dexamethasone in both subcutaneous and omental adipose tissue of men and women (r=0.24, n=26, p=0.01).[22]

The glucocorticoid-*AKR1C2* pathway may generate essential environmental weakness because any environmental factor that raises glucocorticoid levels or boosts glucocorticoid receptor function will lead to increased *AKR1C2* production in *rs28571848* carriers which results in more severe androgen degradation and increased fat formation.[22,25]

Environmental obesogens: polycyclic aromatic hydrocarbons and* AKR1C *transactivation

Environmental factors that drive transactivation of *AKR1C1* and *AKR1C2* were discovered after establishing that rare mutations in both genes cause familial lipedema and common regulatory polymorphisms create population-level susceptibility to disease. [26]

Polycyclic Aromatic Hydrocarbons (PAHs) provide evidence of environmental *AKR1C* induction in cell culture models, though the relevance to human lipedema pathogenesis requires further investigation. Burczynski and Penning conducted a study in HepG2 cells which showed that exposed to benzo[a]pyrene and other PAHs showed a 3- to 10-fold increase in both *AKR1C* mRNA and protein levels which resulted in higher enzymatic activity.[28] The induction process operates through specific isoforms because RNase protection assays showed that *AKR1C1* mRNA functions as the transcript which gets upregulated by both mono- and bi-functional inducers together with reactive suggest Reactive Oxygen Species (ROS) in human hepatoma (HepG2) and colon

carcinoma (HT29) cells which creates a direct link between air pollution and the specific enzyme that causes familial lipedema.[28]

The PAH-derived electrophilic metabolites together with reactive oxygen species drive Nrf2 transcription factor activation which interacts with Antioxidant Response Elements (ARE) that exist in the *AKR1C1* promoter region.[29] The induction process uses ARE for mediation because it does not use Xenobiotic Response Elements (XRE), which creates a difference between it and cytochrome P450 induction. The *AKR1C* enzymes display the highest levels of expression among all human genes which the Keap1/Nrf2 pathway controls when Nrf2 activators are used.[29]

The biochemical effects of the process begin with enzyme activation which leads to oxidative stress development through nonproductive redox reactions. The *AKR1C* enzymes oxidize PAH trans-dihydrodiols into corresponding o-quinones which generate reactive oxygen species during this process.[30] The PAH o-quinones function as Michael acceptors which possess redox-active properties to create nonproductive redox cycles that result in increased ROS production. The *AKR1C1* reaction produces benzo[a]pyrene-7,8-dione BPQ which acts as an electrophilic redox-cycling product that activates *AKR1C1* expression. This reaction resulted in two types of amplification, including chemical redox-cycling and genetic *AKR1C1* induction resulted in ROS production in PAH-exposed cells.[28,30]

Epidemiological evidence demonstrates associations between air pollution and fat mass development, though these studies were conducted in general populations without specific assessment of lipedema. The study investigated 1,654 midlife women from the SWAN cohort. The results showed that higher PM2.5 levels which increased by one interquartile range were associated with fat mass increase of 4.53% and higher fat mass proportion to increase of 1.10% and lean mass to decrease of 0.39%. The study found that fat mass showed stronger associations

with PM2.5 than BMI measurements which indicated that adipose tissue accumulation occurred preferentially.[31] Meta-analysis of general obesity studies confirmed that PM2.5 and NO_2 create positive correlations with obesity according to the results of several meta-analyses. One study found that every PM2.5 increment resulted in 0.93 kg/m² higher BMI.[32,33] However, these associations derive from general obesity research and their specific relevance to lipedema pathogenesis remains to be established.

Endocrine-disrupting chemicals: steroid metabolism disruption and **AKR1C** *pathway convergence*

Phthalates and bisphenols have been shown to disrupt steroidogenesis in cell culture models, though the clinical relevance to human lipedema requires further investigation. The H295R steroidogenesis assay showed that plasticizers at food-relevant concentrations (0.25-25 μM) caused a significant increase in estradiol levels while decreasing testosterone levels, which resulted in a shift of steroid biosynthesis toward estrogen production.[1] The quantitative PCR and Western blot analyses showed that Mono(2-Ethylhexyl) Phthalate (MEHP) caused *17β-HSD1* and *CYP19A1* (aromatase) to increase in expression while it caused *CYP17A1*, *CYP11A1*, and *StAR* to decrease in expression.[1] Multiple phthalates and their metabolites disrupt sex hormone balances through modulating key steroidogenic genes, with significant down-regulation of *StAR* gene and up-regulation of *CYP19A* gene.[13]

The bisphenol analogues (BPA, BPF, BPS, and BPAF) decrease all measured androgen levels while they increase estradiol.[34] In adipocyte differentiation models, environmental obesogens bisphenols phthalates and parabens control adipogenic transcription factors to activate adipocyte

differentiation even without dexamethasone, which produces adipogenic results through *PPARγ C/EBPα* and *FABP4* expression induction.[35]

Studies in mesenchymal stem cell models suggest that environmental endocrine disruptors may play a role in lipedema pathogenesis by disrupting the adipogenic differentiation process of mesenchymal stem cells during specific time periods between their development stages.[36] The substances BPA DEHP and Tributyltin (TBT) control adipogenic differentiation through their concentration levels and developmental stages and different compounds, except TBT which promotes adipogenesis during all developmental stages that we examined.[36] Epidemiological studies demonstrate associations between phthalates and bisphenol A exposure and and obesity risk, with some evidence suggesting that prenatal exposure to these substances affects metabolic functions through epigenetic pathways which leads to obesity development in future generations.[37] However, these studies examined general obesity outcomes in populations not specifically assessed for lipedema.

The observed hormonal shifts in experimental models, increased estrogens and progesterone with decreased androgens, parallel patterns seen with *AKR1C* genetic variants, suggesting potential interactions between EDC exposure and genetic factors in lipedema pathogenesis, though direct evidence in lipedema patients is lacking.[1,3,5]

Hormones in beef: exogenous steroid exposure and* AKR1C *interactions

Agricultural practices permit use of hormonal growth promotants in cattle: 17β-estradiol testosterone progesterone trenbolone acetate zeranol and melengestrol acetate.[38] The compounds exhibit oestrogenic androgenic and progestogenic effects which cattle breeders use to achieve better weight gains and muscle growth while decreasing their animals fat development.[38]

Researchers used dietary surveys from across the nation together with actual hormone measurements taken from 397 retail beef samples to estimate human consumption rates of hormonal growth promotants found in beef products.[35] The highest estimated hazard quotients were found for Melengestrol Acetate (MGA) because the 99th percentile of short-term intake among young boys equaled or exceeded the acceptable daily intake under maximum exposure scenarios.[35]

The potential significance for lipedema is hypothesized as follows: in *AKR1C1* loss-of-function carriers, reduced capacity to inactivate progesterone could mean dietary progestins accumulate to higher local concentrations in adipose tissue, potentially exaggerating pro-adipogenic signaling.[3] In rs28571848 carriers with enhanced *AKR1C2* expression, dietary testosterone or trenbolone might would be more rapidly inactivated to weak androgen receptor agonists, reducing anti-adipogenic androgen signaling.[22,25] However, direct evidence linking dietary hormone exposure from beef to lipedema development is currently lacking.

Concerns about safety of hormone residues in meat have been raised by Andersson and Skakkebaek, who re-evaluated the *JECFA* conclusions and found that they were based on uncertain assumptions, particularly regarding prepubertal children who may be particularly sensitive to low levels of estradiol.[39] The data on residue levels in meat were based on studies performed in the 1970s and 1980s using radioimmunoassay methods with generally inadequate sensitivity, and reliable data on daily production rates of steroid hormones were and are still lacking in healthy prepubertal children.[39] Environmental factors influencing the *AKR1C* pathway, their mechanisms, and levels of evidence are summarized in Table 2.

Epigenetic regulation of AKR1C *enzymes: persistent reprogramming*

Lipedema displays three main characteristics which start during puberty or pregnancy and develop over time while resisting weight loss through dieting. Persistent environmental changes may result in physical alterations potentially through lasting epigenetic changes which affect *AKR1C* gene function. The expression of *AKR1C* in adipose tissue depends on two main mechanisms of epigenetic control. Ostinelli *et al.* identified that rs28571848 and rs34477787 are located on binding sites of glucocorticoid receptor and RORα, mapping to regions with active chromatin marks in adipose tissue.[22,25] The regulatory variants suggest that epigenetic changes at these specific locations have the power to control *AKR1C2* gene expression based on environmental factors. The development of obesity and metabolic disorders into white adipose tissue begins through epigenetic processes which nutrients and lifestyle choices control to determine how adipose tissue develops and functions.[40]

Epigenetics includes mechanisms by which the cell can adapt the cellular response to environmental conditions and alterations in metabolic pathways that occur during obesity lead to disruptions in adipose tissue epigenetic marks.[40] The process of adipogenesis requires both transcriptional control and epigenomic control which needs *PPARγ* and *C/EBPα* to function as lineage-influencing transcription factors together with various epigenomic control elements that include histone methylation and histone acetylation and chromatin remodeling and DNA methylation and microRNAs as their control elements.[41]

Evidence of epigenetic regulation of key steroidogenic enzymes is increasing, with steroid hormones exerting their action through nuclear receptors that are more likely to be epigenetically regulated than proteins involved in steroidogenesis.[42] Environmental exposures can epigenetically reprogram adipocyte fate and function, mainly by altering DNA methylation and histone

modification patterns, with transcription factors and chromatin-modifying coregulator complexes coordinating both signaling-induced transcriptional and epigenetic alterations.[21]

These epigenetic mechanisms may help explain how developmental exposures produce latent disease onset at puberty or pregnancy, the characteristic hormonal triggers of lipedema , though direct evidence in lipedema patients is needed.[3,5,37]

Limitations of current evidence on environmental factors

The evidence linking environmental obesogens to lipedema pathogenesis has several important limitations. First, most mechanistic data derive from *in vitro* cell culture models (HepG2, H295R, 3T3-L1) or general obesity models rather than lipedema-specific experimental systems. The doses used in experimental studies (e.g., 0.25-25 μM for phthalates, 1 μM dexamethasone) may not reflect typical human exposure levels, and extrapolation from cell culture to human adipose tissue requires caution. Second, epidemiological associations between air pollution or EDCs and obesity were established in general populations without lipedema assessment, limiting direct applicability. Third, the proposed mechanisms linking dietary hormones in beef to lipedema are largely theoretical, lacking direct clinical evidence. Fourth, while PAH exposure induces *AKR1C1* in hepatoma cells, whether similar induction occurs in human subcutaneous adipose tissue at environmentally relevant exposures remains unknown. Finally, the epigenetic reprogramming hypothesis, while biologically plausible, requires validation through longitudinal studies examining environmental exposures, epigenetic marks, and lipedema development in at-risk populations.

Discussion

The discovery of *AKR1C1* and *AKR1C2* mutations in ultra-rare familial lipedema has illuminated a potential the pathophysiological pathway underlying this prevalent multifactorial disease.[3] The steroidomic evidence suggests: *AKR1C1 and AKR1C2* influence local steroid balance, potentially shifting the adipose microenvironment toward a pro-adipogenic state.[22,40] This research work advances a unified gene–environment model where lipedema may arise from the convergence of multiple mechanisms acting on the *AKR1C* pathway, as summarized in Figure 1.

Genetic susceptibility operates across a spectrum from ultra-rare coding mutations (*AKR1C1 p.Leu213Gln, AKR1C2 Ser320PheTer2*) with large effects to common regulatory polymorphisms (rs28571848, rs34477787) with smaller effects, creating a continuum from monogenic familial lipedema to polygenic population susceptibility.[3-5,25] The identification of eight additional *AKR1C1* polymorphisms in population databases suggest that common variants in the same genes create widespread predisposition.[4]

Environmental factors may amplify genetic susceptibility through multiple mechanisms that ultimately converge on the *AKR1C* pathway: in cell culture models, PAHs lead to a 3-10 fold increase in *AKR1C1* expression through Nrf2-ARE pathways experimental studies show phthalates with bisphenols drive steroid production toward estrogen while they enhance adipose tissue development and beef contains hormones that deliver external steroids which may interact with combine with genetically determined *AKR1C* metabolic activity.[1,28,29,35,37,38] Evidence suggests that environmental exposures induce DNA methylation together with histone modifications that affect steroid metabolism gene expression because regulatory variants map to areas where active chromatin marks exist.[21,25,40,42] These mechanisms may collectively shift local steroid signaling toward a pro-adipogenic profile. The helps explain lipedema epidemiological patterns because high prevalence affects approximately 11% of women which results from both

polygenic genetics and environmental exposures that occur throughout the population. Variable gene penetrance may reflect interactions between genetic and environmental factors with genetic characteristics. People start to develop this condition when they reach hormonal milestones that coincide with the accumulation of obesogenic substances in their bodies. Resistance to dietary interventions may reflect the influence of environmental factors than the number of calories consumed. Clinically, this framework may help explain key features of lipedema, including its onset during hormonally sensitive periods, its resistance to caloric restriction, and its progression toward lipo-lymphedema in advanced stages. From a clinical perspective, the diagnosis of lipedema remains primarily based on clinical evaluation, including characteristic fat distribution, tenderness, and resistance to weight loss. However, imaging techniques may support differential diagnosis in selected cases. In particular, lymphoscintigraphy can be useful when a mixed lipedema-lymphedema phenotype is suspected or when assessment of lymphatic function is clinically relevant.[43] Although the *AKR1C*-centered model is not yet ready for routine clinical application, it may inform future approaches to patient stratification, biomarker development, and targeted prevention strategies.

Conclusions

Lipedema appears to be a multifactorial disease in which ultra-rare familial mutations have highlighted a potentially critical role for the *AKR1C* pathway, common polymorphisms may contribute to population-level susceptibility, and environmental obesogens may contribute to the transition from genetic predisposition to clinical disease.

Through direct enzyme induction, steroid metabolism disruption, and epigenetic reprogramming. The gene-environment framework provides a plausible mechanistic model that may help explain

lipedema as a multifactorial disease with identifiable molecular pathways, opening directions for: (i) precision diagnostics through *AKR1C* genotyping to identify high-risk individuals; (ii) targeted therapeutics modulating steroid metabolism or *AKR1C* activity; (iii) primary prevention through reduction of environmental obesogen exposures, particularly during critical developmental windows. Further research is needed to validate the environmental components of this model through lipedema-specific studies examining obesogen exposures, *AKR1C* expression in affected tissues, and gene-environment interactions in well-characterized patient cohorts.

References

1. Cifarelli V. Lipedema: progress, challenges, and the road ahead. Obes Rev 2025;26:e13953.

2. Morgan S, Reid I, Bendon C, et al. A family-based study of inherited genetic risk in lipedema. Lymphat Res Biol 2024;22:106-11.

3. Kaftalli J, Bonetti G, Marceddu G, et al. AKR1C1 and hormone metabolism in lipedema pathogenesis: a computational biology approach. Eur Rev Med Pharmacol Sci 2023;27:137-47.

4. Kruglikov IL, Joffin N, Scherer PE. The MMP14-caveolin axis and its potential relevance for lipoedema. Nat Rev Endocrinol 2020;16:669-74.

5. Lüchinger JE, Pavicic E, Giachino CL, Stute P. Impact of hormones on lipedema development: a systematic literature review. Arch Gynecol Obstet 2026;313:60.

6. Forner-Cordero I, Szolnoky G, Forner-Cordero A, Kemény L. Lipedema: an overview of its clinical manifestations, diagnosis and treatment of the disproportional fatty deposition syndrome - systematic review. Clin Obes 2012;2:86-95.

7. Choudhary S, Dubey A, Singh A, et al. Engineering the microenvironment: advanced biomaterials for humanized in vitro immunotoxicology and carcinogenicity assessment. Explor BioMat-X 2025;2:101351.

8. Langendoen SI, Habbema L, Nijsten TEC, Neumann HAM. Lipoedema: from clinical presentation to therapy. A review of the literature. Br J Dermatol 2009;161:980-6.

9. Okhovat JP, Alavi A. Lipedema. Int J Low Extrem Wounds 2015;14:262-7.

10. Tomlinson DJ, Erskine RM, Morse CI, et al. The impact of obesity on skeletal muscle strength and structure through adolescence to old age. Biogerontology 2016;17:467-83.

11. Buso G, Depairon M, Tomson D, et al. Lipedema: a call to action! Obesity (Silver Spring) 2019;27:1567-76.

12. Mortada H, Alhithlool AW, AlBattal NZ, et al. Lipedema: clinical features, diagnosis, and management. Arch Plast Surg 2025;52:185-96.

13. Child AH, Gordon KD, Sharpe P, et al. Lipedema: an inherited condition. Am J Med Genet A 2010;152A:970-6.

14. Michelini S, Herbst KL, Precone V, et al. A multi-gene panel to identify lipedema-predisposing genetic variants by a next-generation sequencing strategy. J Pers Med 2022;12:268.

15. Klimentidis YC, Chen Z, Gonzalez-Garay ML, et al. Genome-wide association study of a lipedema phenotype among women in the UK Biobank identifies multiple genetic risk factors. Eur J Hum Genet 2023;31:338-44.

16. Zakeri M, Safaiee MS, Taheri F, et al. Secondary findings from whole-exome sequencing data in families with familial combined hyperlipidemia (FCHL). Egypt J Med Hum Genet 2021;22:79.

17. Santella B, Salvati A, Papp A, et al. Epigenetic alterations of AKT1 orchestrate a metabolic reprogramming in advanced lipedema: translational insights from an integrated multi-omics study. J Transl Med 2026;24:265.

18. Katzer K, Hill JL, McIver KB, Foster MT. Lipedema and the potential role of estrogen in excessive adipose tissue accumulation. Int J Mol Sci 2021;22:11720.

19. Kaftalli J, Donato K, Bonetti G, et al. Aldo-keto reductase 1C2 (AKR1C2) as the second gene associated to non-syndromic primary lipedema: investigating activating mutation or overexpression as causative factors. Eur Rev Med Pharmacol Sci 2023;27:13227-35.

20. Blouin K, Veilleux A, Luu-The V, Tchernof A. Androgen metabolism in adipose tissue: recent advances. Mol Cell Endocrinol 2009;301:97-103.

21. Ostinelli G, Vijay J, Vohl MC, et al. AKR1C2 and AKR1C3 expression in adipose tissue: association with body fat distribution and regulatory variants. Mol Cell Endocrinol 2021;527:111220.

22. Ostinelli G, Ramalho A, Gauthier MF, et al. Impact of AKR1C2 and AKR1C3 single-nucleotide polymorphism rs28571848 in adipose tissues of individuals with severe obesity. Am J Physiol Endocrinol Metab 2026;330:E276-86.

23. Blouin K, Nadeau M, Mailloux J, et al. Pathways of adipose tissue androgen metabolism in women: depot differences and modulation by adipogenesis. Am J Physiol Endocrinol Metab 2009;296:E244-55.

24. Blouin K, Blanchette S, Richard C, et al. Expression and activity of steroid aldoketoreductases 1C in omental adipose tissue are positive correlates of adiposity in women. Am J Physiol Endocrinol Metab 2005;288:E398-404.

25. Burczynski ME, Lin HK, Penning TM. Isoform-specific induction of a human aldo-keto reductase by polycyclic aromatic hydrocarbons (PAHs), electrophiles, and oxidative stress: implications for the alternative pathway of PAH activation catalyzed by human dihydrodiol dehydrogenase. Cancer Res 1999;59:607-14.

26. Chivukula N, Madgaonkar SR, Marigoudar SR, et al. TICToK: a comprehensive knowledgebase of tattoo ink chemicals and investigation of their associated toxicities and regulations. 2025. Available from: https://www.biorxiv.org/content/10.1101/2025.08.02.668261v1.full

27. Penning TM. Aldo-keto reductase regulation by the Nrf2 system: implications for stress response, chemotherapy drug resistance, and carcinogenesis. Chem Res Toxicol 2017;30:162-76.

28. Duan C, Fang Y, Sun J, et al. Effects of fast food packaging plasticizers and their metabolites on steroid hormone synthesis in H295R cells. Sci Total Environ 2020;726:138500.

29. Pötzl B, Kürzinger L, Kendl S, et al. Disruptive effects of plasticizers bisphenol A, F, and S on steroidogenesis of adrenocortical cells. Front Endocrinol 2024;15:1387133.

30. Galbraith H. Hormones in international meat production: biological, sociological and consumer issues. Nutr Res Rev 2002;15:293-314.

31. Andersson AM, Skakkebaek NE. Exposure to exogenous estrogens in food: possible impact on human development and health. Eur J Endocrinol 1999;140:477-85.

32. Wang X, Karvonen-Gutierrez CA, Gold EB, et al. Longitudinal associations of air pollution with body size and composition in midlife women: the Study of Women's Health Across the Nation. Diabetes Care 2022;45:2577-84.

33. Furlong MA, Klimentidis YC. Associations of air pollution with obesity and body fat percentage, and modification by polygenic risk score for BMI in the UK Biobank. Environ Res 2020;185:109364.

34. Luta X, Buso G, Porceddu E, et al. Clinical characteristics, comorbidities, and correlation with advanced lipedema stages: a retrospective study from a Swiss referral centre. PLoS One 2025;20:e0319099.

35. Kiani AK, Mor M, Bernini A, et al. Steroid-converting enzymes in human adipose tissues and fat deposition with a focus on AKR1C enzymes. Eur Rev Med Pharmacol Sci 2021;25:7698-706.

36. Stel J, Legler J. The role of epigenetics in the latent effects of early life exposure to obesogenic endocrine disrupting chemicals. Endocrinology 2015;156:3466-72.

37. Heindel JJ, Howard S, Agay-Shay K, et al. Obesity II: establishing causal links between chemical exposures and obesity. Biochem Pharmacol 2022;199:115015.

38. Janesick AS, Blumberg B. Obesogens: an emerging threat to public health. Am J Obstet Gynecol 2016;214:559-65.

39. Penning TM, Wangtrakuldee P, Auchus RJ. Structural and functional biology of aldo-keto reductase steroid-transforming enzymes. Endocr Rev 2019;40:447-75.

40. Veilleux A, Côté JA, Blouin K, et al. Glucocorticoid-induced androgen inactivation by aldo-keto reductase 1C2 promotes adipogenesis in human preadipocytes. Am J Physiol Endocrinol Metab 2012;302:E941-9.

41. Tchernof A, Mansour MF, Pelletier M, et al. Updated survey of the steroid-converting enzymes in human adipose tissues. J Steroid Biochem Mol Biol 2015;147:56-69.

42. Rižner TL, Penning TM. Role of aldo-keto reductase family 1 (AKR1) enzymes in human steroid metabolism. Steroids 2014;79:49-63.

43. Eretta C, Di Pumpo F, Bizzarri S, et al. Does lymphoscintigraphy have a role in the diagnosis and management of lipedema? Veins Lymphat 2025;14:14438.

Contributions: conceptualization, MB; methodology, JK, KD, LF; investigation, DV, BDF, DV, SeM, SaM, SiM, MB; writing - original draft, DV, JK, LF, KD, BDF; writing - review & editing, MB, DV, DV, SaM, SeM, SiM; project administration, MB. All the authors have read and approved the final version of the manuscript, and agreed to be held accountable for all aspects of the work.

Conflict of interest: all affiliations of the authors with private companies have been declared to make clear the position regarding the interests of these companies. The authors are affiliated with private companies for which there could be a possible conflict of interest. The authors of this article are reported to be owners of patents.

Funding: none.

Ethics approval and consent to participate: not applicable.

Informed consent: not applicable.

Patient's consent for publication: not applicable.

Availability of data and materials: all data generated or analyzed during this study are included in this published article.

Table 1. Genetic variants in *AKR1C* genes associated with lipedema

Gene	Variant	Type	Functional effect	Evidence level	Notes
AKR1C1	p.Leu213Gln	Loss-of-function	Decrease progesterone inactivation (~50%)	Strong (familial)	Causes local progesterone accumulation[3]
AKR1C1	Regulatory polymorphisms	Regulatory	Altered gene expression	Moderate (population)	Population susceptibility[4]
AKR1C2	Ser320PheTer2	Gain-of-function	Increase DHT inactivation	Strong (familial)	Reduces anti-adipogenic signaling[4]
AKR1C2	Overexpression	Expression	Increase enzyme activity	Moderate	Observed in ~24% of patients[4]
AKR1C2/3	rs28571848	Regulatory	GR-mediated increase expression	Moderate-strong	Associated with trunk fat mass[25]
AKR1C2	rs34477787	Regulatory	Transcriptional modulation	Moderate	Affects androgen metabolism[25]

Table 2. Environmental factors influencing the *AKR1C* pathway in lipedema.

Environmental factor	Mechanism of action	Evidence type	Strength of evidence	Relevance to lipedema
Polycyclic Aromatic Hydrocarbons (PAHs)	Nrf2–ARE activation → increase *AKR1C1* expression; ROS generation via quinone redox cycling	*In vitro* (non-adipose cell models: HepG2, HT29)	Moderate	Indirect; no lipedema-specific studies[28,30]
Air pollution (PM2.5, NO_2)	Associated with increased fat mass and altered body composition in epidemiological studies	Epidemiological (general population)	Moderate	Indirect; not evaluated in lipedema cohorts[32,33]
Phthalates (e.g., MEHP)	Disruption of steroidogenesis: increase aromatase (*CYP19A1*), decrease androgen synthesis (*CYP17A1, StAR*)	*In vitro* (*H295R*)	Moderate	Indirect; obesity-based evidence[28]
Bisphenols (BPA, BPF, BPS)	Decrease androgens, increase estrogens; activation of adipogenic transcription factors (*PPARγ, C/EBPα*)	*In vitro*	Moderate	Indirect; no lipedema-specific validation[29]
Obesogens (BPA, TBT, DEHP)	Induction of adipocyte differentiation;	*In vitro*/developmental models	Moderate	Hypothesized role in lipedema[36,37]

	epigenetic reprogramming			
Dietary hormones (beef-derived steroids)	Hypothesized interaction with *AKR1C*-mediated steroid metabolism	Exposure assessment studies	Low	Theoretical; no direct evidence in lipedema[30,31]
Glucocorticoid signaling	GR activation → increase *AKR1C2* expression → increase DHT inactivation	Human adipose tissue and mechanistic studies	Moderate-strong	Potentially relevant in genetically susceptible individuals[22,40]

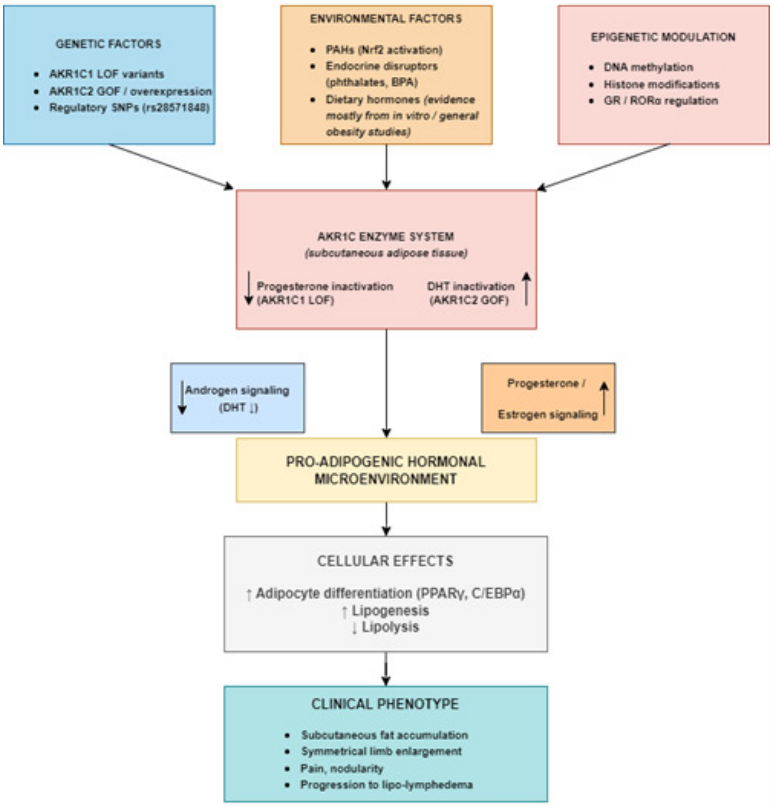

Figure 1. Schematic representation of the *AKR1C*-centered gene–environment model of lipedema pathogenesis. Genetic variants, environmental factors, and epigenetic mechanisms converge on *AKR1C* enzyme activity in subcutaneous adipose tissue, leading to altered steroid metabolism, a pro-adipogenic hormonal microenvironment, and the development of characteristic clinical features.