Chapter

Lipedema: A Painful Adipose Tissue Disorder

Sara Al-Ghadban, Karen L. Herbst and Bruce A. Bunnell

Abstract

Lipedema is a painful fat disease of loose connective tissue usually misdiagnosed as lifestyle-induced obesity that affects ~10% of women of European descent as well as other populations. Lipedema is characterized by symmetric enlargement of the buttocks, hips, and legs due to increased loose connective tissue; arms are also affected in 80% of patients. Lipedema loose connective tissue is characterized by hypertrophic adipocytes, inflammatory cells, and dilated leaky blood and lymphatic vessels. Altered fluid flux through the tissue causes accumulation of fluid, protein, and other constituents in the interstitium resulting in recruitment of inflammatory cells, which in turn stimulates fibrosis and results in difficulty in weight loss. Inflammation and excess interstitial substance may also activate nerve fibers instigating the painful lipedema fat tissue. More research is needed to characterize lipedema loose connective tissue structure in depth, as well as the form and function of blood and lymphatic vessels. Understanding the pathophysiology of the disease will allow healthcare providers to diagnose the disease and develop treatments.

Keywords: lipedema, symptoms, diagnosis, treatment, blood vessels, lymphatics

1. Introduction

Loose connective tissue disorders include lipedema, Dercum's disease (DD), familial multiple lipomatosis (FML) and multiple symmetric lipomatosis (MSL). All these disorders share many similarities with lipedema including painful lipomas, obesity, fibrosis, a risk of developing lymphedema and difficulty in losing the abnormal fat through diet and exercise. There are clinical characteristics specific for lipedema, including the onset of the disease, fat location and associated health issues (**Table 1**) [1, 2].

Lipedema is often misdiagnosed as lifestyle-induced obesity that affects ~10% of women of European descent as well as other populations [3, 4]. Although both disorders are considered inflammatory diseases due to the presence of increased macrophages and hypertrophic adipocytes, there are significant differences between the two disorders. Among these is the location of the fat, primarily abdominal or spread widely over the body in obesity compared to the symmetric distribution in the lower extremities in lipedema, the texture of the skin (thin and soft in lipedema and thicker in obesity), easy bruising and pain upon the introduction of pressure in lipedema [5, 6].

Characteristic	Lipedema	DD	MSL	FML	MSL
Abnormal fat location	Legs, arms, abdomen	Global	Upper; can be global	Arms, thighs, trunk, abdomen	Upper; can be global
Diet-resistant fat	Yes	Yes	Yes	Yes	Yes
Lipomas	Yes	Common	Common in men	Common	Common in men
Time fat change	Puberty; 3rd decade	Child-adult	Adult; child rare	Child-adult	Adult; child rare
Painful fat	Yes	Yes	Not usually	Lipoma	Not usually
Sex predominance	Female	Female	Male	Male = female	Male
Lymphatic dysfunction	Yes	Yes	Yes	Yes	Yes
Prevalence	Possibly common	Possibly common	Rare	Rare	Rare
Associated conditions	Lymphedema	Autoimmune; diabetes	Neuropathy	Moles; neuropathy	Neuropathy
Inheritance pattern	Autosomal dominant; incomplete penetrance	Autosomal dominant; sex-specific influence	Autosomal dominant or recessive	Autosomal dominant	Autosomal dominant or recessive

Modified from Ref. [1].

Table 1.
Characteristics of loose connective tissue disorders.

The focus of this review will be on the disease of lipedema, different stages and types, diagnosis and treatment, pathogenesis and current research in the field.

2. Lipedema

Lipedema also referred to as lipedema, is a painful loose connective tissue disorder first described in 1940 by Allen and Hines [7]. Lipedema is characterized by symmetric enlargement of the buttocks, hips and legs due to deposition of loose connective tissue that includes fascia, adipocytes, immune cells and other structures; arms are also affected in 80% of patients [3, 4]. Feet are typically spared, but ankle cuffs are often noted in advanced stages of lipedema where the risk of lymphedema is also high [8, 9]. Patients with lipedema experience mobility issues, psychosocial distress, anxiety, eating disorders, sleep apnea and depression [1, 10].

Lipedema is considered a hormone-related disorder affecting almost exclusively women during puberty, childbirth or menopause. Case reports of men with lipedema have been described in literature. Men with lipedema have elevated estrogen level and low to absent testosterone levels resulting in cirrhosis, gynecomastia and hypogonadism [11–13]. While the exact etiopathogenesis of this disease is unknown [10, 14], many studies have demonstrated that inflammatory cells, hypertrophic adipocytes, abnormal blood vessels and lymphatic dysfunction are associated with tissue damage and development of a fibrotic disease [14–17].

2.1 Stages of lipedema

Lipedema consists of three stages characterized by the texture of skin and tissue formation. Stage 1 involves smooth skin over pearl-sized nodules in a hypertrophic fat layer; Stage 2 has skin indentations over a hypertrophic fat structure of pearl-to-apple-size masses; and Stage 3 includes pearl-sized nodules and much larger fat masses causing lobules of skin and fat to form mainly on the hips, thighs, and around the knees. Lymphedema, causing fluid accumulation in the limbs, may develop during any stage of lipedema and is referred to as lipo-lymphedema [1, 3, 10, 18, 19].

Healthcare providers often misdiagnose women with lipedema as they do not take into account the disproportionate size of the legs compared to trunk especially in Stage 1 and 2 along with the inability to lose fat from areas affected by lipedema. It is possible to confuse women with Stage 3 lipedema as having lifestyle-induced obesity due to fat involving more areas of the body.

2.2 Types of lipedema

In addition to stages of lipedema, lipedema is also characterized by types determined by the area of the body that is affected. There are five types of lipedema; types I, II, and III are the most common. In Type I, fat is deposited in the areas of the buttocks and hips resembling saddle bags. In Type II, fat extends to the knees from the buttocks area with the formation of folds of fat around the inside of the knee. In Type III, fat spreads all over the lower body from the hips to the ankles. In Type IV, upper arms are affected causing difficulty in lifting the arm and stress on the shoulder. In Type V, fat is restricted to the lower legs. It is worth noting that patients with lipedema can clinically present with a mixture of types [3, 10].

2.3 Signs and symptoms

Pain, tenderness, bruising easily, symmetrical swelling of the legs, heaviness of affected limbs, burning sensations in the skin and fat, soft skin, negative stemmer's sign and hypermobile joints are among the common symptoms observed in lipedema patients [2, 3, 6, 13]. Hypermobility in women with has been reported to contribute to joint damage and increase the risk of cardiovascular disease as seen in Ehlers Danlos Syndrome-Hypermobility Type (EDS-HT) with Beighton score higher than 5 [2, 3, 20, 21]. Thus, hypermobility causes structural changes in lipedema tissue resulting in increased fibrosis, dysfunction of blood vessels and accumulation of interstitial fluid.

Women with lipedema also experience emotional symptoms due to unexplained weight gain including embarrassment, anxiety and depression that impact their overall quality of life [22, 23]. Symptoms may progress in advanced stages of lipedema that might be associated with increased cardiovascular and renal diseases. A study conducted by Herbst el al. in 2015 provides a detailed list of symptoms experienced by lipedema patients [3].

2.4 Diagnosis and treatment of lipedema

Diagnosis of lipedema involves a comprehensive physical exam based on the criteria listed by Wold and colleagues in 1951, [4] medical and surgical history, list of medications that might affect weight or fluid retention and family history. A physical examination includes assessment of the enlarged lower extremities carefully noting the texture of the affected areas such as velvety soft skin that can be found in hypermobility, nodular fat, pain when applying pressure, tenderness upon

palpation and accumulation of fluid such as pitting or non-pitting edema which may indicate lymphedema [18, 24]. Bruising caused by increased capillary fragility [6], spider veins and telangiectasia showing on the surface of the skin due to venous insufficiency are also observed in lipedema patients [4, 10].

Although, there is no cure for lipedema, treatments like liposuction (tumescent and water jet) [25], complete decongestive therapy that includes manual lymphatic drainage [26, 27], compression garments, a healthy diet, physical activity, medications and supplements (statins, selenium, diosmin, amphetamines and butcher's broom) have been shown to reduce pain, improve lymphatic function, decrease leakage from blood vessels, lessen inflammation and fibrosis and maintain a healthy gut [24, 28–34].

Liposuction is by far the most effective treatment to decrease the fibrotic lipedema fat and thereby maintain mobility which is essential for the welfare of women living with lipedema [35–37]. Water jet-assisted liposuction has been proven to be as effective as tumescent liposuction. Damage to the lymph vessels has not been show as evidenced in a histological study conducted by Stutz et al. on lipoaspirates collected from lipedema patients [32]. Nevertheless, special care should be taken with lipo-lymphedema patients, where accumulated lymph and or fibrotic tissue should be removed first. Furthermore, follow-up and compression therapy are advised for successful and effective treatment.

Deep tissue massage has also been demonstrated to improve the quality of subcutaneous adipose tissue by decreasing pain, fibrosis and fat tissue in women with lipedema [29, 38].

Additionally, a healthy non-inflammatory diet is highly recommended, even though it will not reduce the lipedema tissue, but it might slow the progression of the disease by reducing inflammation and pain, lessen the swelling and ultimately improve quality of life. No one plan works for everyone but a ketogenic diet with low processed carbohydrate and mild physical exercises like walking, swimming, Pilates, yoga and other home excise programs are suggested by lipedema specialists. These activates will help the function of lymphatic pump and maintain a normal metabolism.

Finally, it is very important to detect and treat lipedema at early stages thus preventing the complications that might occur due to the progression of disease. These complications comprise eating disorders, sleep apnea, diabetes mellitus, arthritis, hypertension, cellulitis, cardiac and renal disease.

3. Lipedema versus lymphedema

There are distinctive criteria for lipedema which are absent in lymphedema including a negative Stemmer's sign, minimal pitting edema, thin skin, easy bruising, tenderness and pain [14, 39, 40]. Although lymphatic microaneurysms might develop in the later stages of lipedema leading to secondary lymphedema, imaging techniques like high-resolution cutaneous ultrasonography and magnetic resonance imaging showed no defects in the lymphatic system in early stages [24, 41–43]. Other methods have also been successfully used to differentiate lipedema from lymphedema which includes tissue dielectric constant and dual-energy X-ray absorptiometry techniques [44–48].

Dysfunction of lymphatic vessels results in accumulation of interstitial fluid (edema) in adipose tissues triggering inflammation by the recruitment of macrophages resulting in fibrosis and difficulty with weight loss. As a consequence, adipose tissue loses its elasticity suggesting that lipedema might be a connective tissue disorder [15, 49]. Studies have also indicated that edema might induce growth of lipedema fat as well as hypoxia resulting in adipocyte cell death [50].

Further, morphologic changes in lymphatic vessels and accumulation of interstitial fluid are present in some women with lipedema, with no change in transport of lymphatic fluid, which suggests these individuals might have a higher risk of progressing to lipo-lymphedema especially in advanced stages of lipedema [15, 51]. Accurate diagnosis of lipedema in association with lymphedema is essential for treating and following up of lipedema patients.

4. Pathophysiology of the disease

Hormones, genetic factors, leaky blood vessels, dysfunctional lymphatics system, inflammation, hypertrophic adipocytes and interstitial thickening are among the factors that contribute to the pathogenesis of lipedema [10, 12, 15].

4.1 Hormones

Hormones play an essential role in the etiology of the lipedema, but how they affect the metabolism and function of adipocytes function is still unknown. Studies have shown that hormones, like estrogen and progesterone, have a direct effect on lipogenesis, insulin levels and adipose tissue distribution in the body. Dysregulation of hormonal levels lead to fat dysregulation, impairment of the lipogenesis-lipolysis mechanism, hypertension, insulin resistance and hyperinsulinemia [13, 52, 53]. Hormones might also have an impact on the nervous system which might explain the pain experienced by lipedema patients. Szél et al. hypothesized that alteration in estrogen (or estrogen receptors) maybe involved in the pathogenesis of lipedema by suggesting a link between accumulation of adipose tissue, imbalanced estrogen levels and inflammation of the peripheral and sympathetic nerves of the disease [13].

4.2 Adipocytes, immune cells and blood vessels

Lipedema fat tissue is characterized by hypertrophic adipocytes, inflammatory immune cells, dilation of subdermal blood and lymphatic vessels. We and others have shown a high number of infiltrating macrophages in lipedema adipose tissue detected by the CD68 marker and observed as around blood vessels or as crown-like structures surrounding necrotic adipocytes. In addition to macrophages, mast cells and T-lymphocytes were detected in hyper-vascular areas mainly around blood vessels in lipedema fat tissue which might contribute to capillary permeability and accumulation of interstitial fluid [15, 16, 54].

An article published in 2004 by Taylor et al. showed that accumulation of mast cells in lipedema tissue contributed to increased interstitial fluid, deterioration of adipocytes and potentially elastic fiber fragmentation due to the release of elastase [55], confirming that lipedema is a connective tissue disorder. Adding to that, direct cell-cell interaction between hypertrophic adipocyte and macrophages as well as secreted paracrine factors such as vascular endothelial growth factor (VEGF), a marker of angiogenesis, previously reported in the blood of women with lipedema [56] might be associated with increase in the number of blood vessels, dilation of capillaries, hypoxia, inflammation and tissue fibrosis found in lipedema patients [15, 18, 57].

5. Is there a role of adipose-derived stem cells (ASC) in lipedema?

Adipose tissue-derived stem cells are widely studied for their immunomodulatory, anti-inflammatory, anti-fibrotic, anti-apoptotic and pro-angiogenic effects

[58–60], but how ASCs contribute to the development of lipedema has not been investigated yet. Due to their high therapeutic potential, ASCs are now considered an indispensable tool in regenerative medicine [61–64]. Studies have shown the successful treatment with ASCs for many disease including graft-versus-host disease [65], wound healing [66], cardiovascular [67], inflammatory bowel disease [68], diabetes mellitus [69] and several injuries including kidney and spinal cord [70], bone and craniofacial reconstruction [71, 72], liver cirrhosis [73], multiple sclerosis [74]. In addition to their self-renewal ability, ASCs have the ability to differentiate into multiple lineages, including adipocytes, osteoblasts, chondrocytes, and endothelial cells [75, 76]. Thus, ASCs might play a role in lipedema adiposity by inducing the expansion and differentiation of progenitor adipose-derived stem/progenitor cells (pre-adipocytes) into mature adipocytes (hyperplasia). Suga el at. have shown an increase in proliferation of adipose-derived stem/progenitor cell proliferation using Ki67 and CD34 markers suggesting an increase in adipogenesis, hypoxia, and adipocyte necrosis, at least in one case [16].

Adding to that, inflammatory cytokines secreted by hypertrophic adipocytes and factors in the interstitial fluid could stimulate ASC differentiation into mature adipocytes. Alternatively, ASCs produce a plethora of pro- and anti-inflammatory cytokines that might contribute to angiogenesis and inflammation resulting in leaky and fragile blood vessels [77, 78]. Priglinger et al. have characterized lipedema ASCs isolated from liposuction samples and showed an increasing number of endothelial/pericytic cells using CD146 marker in lipedema patients compared to healthy individuals proposing that this increase might be a marker of repair of leaky blood and lymphatic vessels in lipedema tissues [54].

Although, ASCs might induce adipogenesis in lipedema an in-depth characterization of ASCs is required to confirm this theory. Otherwise, if ASCs prove to have anti-inflammatory, anti-fibrotic or pro-angiogenic effects, then they might be used to lessen tissue damage caused by leaky vessels; hence autologous treatment might be a promising tool for lipedema patients.

6. Conclusion

Lipedema is a painful fat disease that should be differentiated from obesity and lymphedema. It is the responsibility of the healthcare provider to determine the accurate diagnosis of the disease for successful treatment and management. Liposuction, hands-on therapy, exercise, and a healthy eating plan are recommended for lipedema patients. Although the etiology of lipedema is complicated, hypertrophic adipocytes, inflammatory cytokines, and macrophages, hypoxia, leaky vessels and accumulation of interstitial fluid contribute to the pathogenesis of the disease and may also help guide treatment.

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Conflict of interest

The authors declare no conflict of interest.

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References

[1] Herbst KL. Rare adipose disorders (RADs) masquerading as obesity. Acta Pharmacologica Sinica. 2012;**33**(2):155-172

[2] Beltran K, Herbst KL. Differentiating lipedema and Dercum's disease. International Journal of Obesity. 2017;**41**(2):240-245

[3] Herbst KL et al. Lipedema fat and signs and symptoms of illness, increase with advancing stage. Archives of Medicine. 2015;**7**:1-8

[4] Wold LE, Hines EA, Allen EV. Lipedema of the legs; a syndrome characterized by fat legs and edema. Annals of Internal Medicine. 1951;**34**(5):1243

[5] Forner-Cordero I et al. Lipedema: An overview of its clinical manifestations, diagnosis and treatment of the disproportional fatty deposition syndrome—Systematic review. Clinical Obesity. 2012;**2**(3-4):86-95

[6] Szolnoky G et al. Measurement of capillary fragility: A useful tool to differentiate lipedema from obesity? Lymphology. 2017;**50**(4):203

[7] Wold LE, Hines EA, Allen EA. Lipedema of the legs: A syndrome characterised by fat legs and orthostatic edema. Proceedings of the Staff Meetings. Mayo Clinic. 1940;**15**:184-187

[8] Shin BW et al. Lipedema, a rare disease. Annals of Rehabilitation Medicine. 2011;**35**(6):922

[9] Szolnoky G, Kemeny L. Lipoedema: From clinical presentation to therapy. Further aspects. The British Journal of Dermatology. 2010;**162**(4):889-889

[10] Torre YS-DL et al. Lipedema: Friend and foe. Hormone Molecular Biology and Clinical Investigation. 2018;**33**(1). DOI: 10.1515/hmbci-2017-0076

[11] Chen S-G et al. Painful fat syndrome in a male patient. British Journal of Plastic Surgery. 2004;**57**(3):282-286

[12] Child AH et al. Lipedema: An inherited condition. American Journal of Medical Genetics Part A. 2010;**152**(4):970-976

[13] Szél E et al. Pathophysiological dilemmas of lipedema. Medical Hypotheses. 2014;**83**(5):599-606

[14] Buck DW, Herbst KL. Lipedema: A relatively common disease with extremely common misconceptions. Plastic and Reconstructive Surgery. Global Open. 2016;**4**(9):e1043

[15] Al-Ghadban S et al. Dilated blood and lymphatic microvessels, angiogenesis, increased macrophages, and adipocyte hypertrophy in lipedema thigh skin and fat tissue. Journal of Obesity. 2019;**2019**:8747461

[16] Suga H et al. Adipose tissue remodeling in lipedema: Adipocyte death and concurrent regeneration. Journal of Cutaneous Pathology. 2009;**36**(12):1293-1298

[17] Lohrmann C, Foeldi E, Langer M. MR imaging of the lymphatic system in patients with lipedema and lipo-lymphedema. Microvascular Research. 2009;**77**(3):335-339

[18] Fife EC, Maus AE, Carter JM. Lipedema: A frequently misdiagnosed and misunderstood fatty deposition syndrome. Advances in Skin & Wound Care. 2010;**23**(2):81-92

[19] Pascucci A, Lynch PJ. Lipedema with multiple lipomas. Dermatology Online Journal. 2010;**16**(9):4

[20] Strunk RG, Pfefer MT, Dube D. Multimodal chiropractic care of pain and disability for a patient diagnosed with benign joint hypermobility syndrome: A case report. Journal of Chiropractic Medicine. 2014;**13**(1):35-42

[21] Beighton P, Grahame R, Bird H. Assessment of Hypermobility. London: Springer London; 2012. pp. 11-26

[22] Alwardat N et al. The effect of lipedema on health-related quality of life and psychological status: A narrative review of the literature. Eat Weight Disorder. 2019. https://doi.org/10.1007/s40519-019-00703-x

[23] Dudek JE et al. Depression and appearance-related distress in functioning with lipedema. Psychology. Health & Medicine. 2018;**23**(7):846-853

[24] Peled AW, Kappos EA. Lipedema: Diagnostic and management challenges. International Journal of Women's Health. 2016;**8**:389

[25] Schmeller W, Hueppe M, Meier-Vollrath I. Tumescent liposuction in lipoedema yields good long-term results. British Journal of Dermatology. 2012;**166**(1):161-168

[26] Szolnoky G et al. Complete decongestive physiotherapy with and without pneumatic compression for treatment of lipedema: A pilot study. Lymphology. 2008;**41**(1):40

[27] Szolnoky G et al. Complex decongestive physiotherapy decreases capillary fragility in lipedema. Lymphology. 2008;**41**(4):161

[28] Okhovat J-P, Alavi A. In: Rerkasem K, editor. Lipedema: A Review of the Literature. Los Angeles, CA: SAGE Journals; 2015. pp. 262-267

[29] Herbst KL, Ussery C, Eekema A. Pilot study: Whole body manual subcutaneous adipose tissue (SAT) therapy improved pain and SAT structure in women with lipedema. Hormone Molecular Biology and Clinical Investigation. 2017;**33**(2). DOI: 10.1515/hmbci-2017-0035

[30] Chuck Ehrlich EI, Herbst KL, Kahn L-A, Sears DD, Kenyon M, McMahon E. Lymphedema and Lipedema Nutrition Guide. Foods, Vitamins, Minerals, and Supplements. San Francisco: Lymph Notes; 2015

[31] Beninson J, Edelglass JW. Lipedema—The non-lymphatic masquerader. Angiology. 1984;**35**(8):506

[32] Stutz J, Krahl D. Water jet-assisted liposuction for patients with lipoedema: Histologic and immunohistologic analysis of the aspirates of 30 lipoedema patients. Aesthetic Plastic Surgery. 2009;**33**(2):153-162

[33] Portillo-Soto A et al. Comparison of blood flow changes with soft tissue mobilization and massage therapy. Journal of Alternative and Complementary Medicine (New York, N.Y.). 2014;**20**(12):932

[34] Macdonald JM, Sims N, Mayrovitz HN. Lymphedema, lipedema, and the open wound: The role of compression therapy. Surgical Clinics of North America. 2003;**83**(3):639-658

[35] Dadras M et al. Liposuction in the treatment of lipedema: A longitudinal study. Archives of Plastic Surgery. 2017;**44**(4):324-331

[36] Brorson H. Liposuction normalizes—In contrast to other therapies—Lymphedema-induced adipose tissue hypertrophy. Handchirurgie, Mikrochirurgie, Plastische Chirurgie. 2013;**44**(06):348-354

[37] Baum S et al. Treatment of lipoedema using liposuction: Results

of our own surveys. Phlébologie. 2015;**44**(3):121-132

[38] Ibarra M et al. Subcutaneous adipose tissue therapy reduces fat by dual X-ray absorptiometry scan and improves tissue structure by ultrasound in women with lipoedema and Dercum disease. Clinical Obesity. 2018;**8**(6):398-406

[39] Shavit E, Wollina U, Alavi A. Lipoedema is not lymphoedema: A review of current literature. International Wound Journal. 2018;**15**(6):921-928

[40] Rudkin G, Miller TA. Lipedema—A clinical entity distinct from lymphedema. Plastic and Reconstructive Surgery. 1994;**94**(6):841-847

[41] Langendoen SI et al. Lipoedema: From clinical presentation to therapy. A review of the literature. British Journal of Dermatology. 2009;**161**:980-986

[42] Fonder MA, Loveless JW, Lazarus G. Lipedema, a frequently unrecognized problem. Journal of the American Academy of Dermatology. 2007;**57**(2):S1-S3

[43] Amann-Vesti B, Franzeck UK, Bollinger A. Microlymphatic aneurysms in patients with lipedema. Lymphology. 2001;**34**(4):170-175

[44] Dimakakos PB et al. MRI and ultrasonographic findings in the investigation of lymphedema and lipedema. International Surgery. 1997;**82**(4):411

[45] Naouri M et al. High-resolution cutaneous ultrasonography to differentiate lipoedema from lymphoedema. British Journal of Dermatology. 2010;**163**(2):296-301

[46] Bräutigam P et al. Analysis of lymphatic drainage in various forms of leg edema using two compartment lymphoscintigraphy. Lymphology. 1998;**31**(2):43

[47] Tuğral A, Bakar Y. An approach to lipedema: A literature review of current knowledge of an underestimated health problem. European Journal of Plastic Surgery. 2019. https://doi.org/10.1007/s00238-019-01519-9

[48] Birkballe S. Can tissue dielectric constant measurement aid in differentiating lymphoedema from lipoedema in women with swollen legs? British Journal of Dermatology. 2014;**170**(1):96-103

[49] Williams A, Macewan I. Accurate diagnosis and self-care support for women with lipoedema. Practice Nursing. 2016;**27**(7):325-332

[50] Martin S, Edward MC, Peter C. Lymph makes you fat. Nature Genetics. 2005;**37**(10):1023

[51] Bilancini S et al. Functional lymphatic alterations in patients suffering from lipedema. Angiology. 1995;**46**(4):333-339

[52] Van Pelt R et al. Acute modulation of adipose tissue lipolysis by intravenous estrogens. Obesity. 2006;**14**(12):2163-2172

[53] Mayes JS, Watson GH. Direct effects of sex steroid hormones on adipose tissues and obesity. Obesity Reviews. 2004;**5**(4):197-216

[54] Priglinger E et al. The adipose tissue: Derived stromal vascular fraction cells from lipedema patients: Are they different? Cytotherapy. 2017;**19**(7):849-860

[55] Taylor NE et al. Tumefactive lipedema with pseudoxanthoma elasticum-like microscopic changes. Journal of Cutaneous Pathology. 2004;**31**(2):205-209

[56] Siems W et al. Anti- fibrosclerotic effects of shock wave therapy in lipedema and cellulite. BioFactors. 2005;**24**(1-4):275-282

[57] Sun K et al. Fibrosis and adipose tissue dysfunction. Cell Metabolism. 2013;**18**(4):470-477

[58] Gimble MJ, Katz JA, Bunnell AB. Adipose-derived stem cells for regenerative medicine. Circulation Research. 2007;**100**(9):1249-1260

[59] Gimble JM et al. Concise review: Adipose-derived stromal vascular fraction cells and stem cells: Let's not get lost in translation. 2011: p. 749-754

[60] Uccelli A, Moretta L, Pistoia V. Mesenchymal stem cells in health and disease. Nature Reviews Immunology. 2008;**8**:726

[61] Frese L, Dijkman PE, Hoerstrup SP. Adipose tissue-derived stem cells in regenerative medicine. Transfusion Medicine and Hemotherapy. 2016;**43**(4):268-274

[62] Konno M et al. Adipose-derived mesenchymal stem cells and. Regenerative Medicine. 2013;**55**:309-318

[63] Ong WK, Sugii S. Adipose-derived stem cells: Fatty potentials for therapy. The International Journal of Biochemistry & Cell Biology. 2013;**45**(6):1083

[64] Schneider S. Adipose-derived mesenchymal stem cells from liposuction and resected fat are feasible sources for regenerative medicine. European Journal of Medical Research. 2017;**22**(1):17

[65] Amorin B et al. Mesenchymal stem cell therapy and acute graft-versus-host disease: A review. Human Cell. 2014;**27**:137-150

[66] Li P, Guo X. A review: Therapeutic potential of adipose-derived stem cells in cutaneous wound healing and regeneration. Stem Cell Research & Therapy. 2018;**9**(1)

[67] White IA et al. Mesenchymal stem cells in cardiology. Methods in Molecular Biology (Clifton, N.J.). 2016;**1416**:55

[68] De Francesco F et al. The role of adipose stem cells in inflammatory bowel disease: From biology to novel therapeutic strategies. Cancer Biology & Therapy; 2016. pp. 889-898

[69] Takahashi H et al. Regenerative and transplantation medicine: Cellular therapy using adipose tissue-derived mesenchymal stromal cells for type 1 diabetes mellitus. Journal of Clinical Medicine. 2019;**8**(2):249

[70] Crigna A et al. Stem/stromal cells for treatment of kidney injuries with focus on preclinical models. Frontiers in Medicine. 2018;**5**:179

[71] Paduano F et al. Adipose tissue as a strategic source of mesenchymal stem cells in bone regeneration: A topical review on the most promising craniomaxillofacial applications. International Journal of Molecular Sciences. 2017;**18**(10):2140

[72] Ciuffi S, Zonefrati R, Brandi ML. Adipose stem cells for bone tissue repair. Clinical Cases in Mineral and Bone Metabolism: The Official Journal of the Italian Society of Osteoporosis, Mineral Metabolism, and Skeletal Diseases. 2017;**14**(2):217

[73] Kwak K-A et al. Current perspectives regarding stem cell-based therapy for liver cirrhosis. Canadian Journal of Gastroenterology & Hepatology. 2018;**2018**. Available from: https://doi.org/10.1155/2018/4197857

[74] Bowles AC et al. Adipose stromal vascular fraction attenuates T1 cell-mediated pathology in a model

of multiple sclerosis. Journal of Neuroinflammation. 2018;**15**(1):77

[75] Bourin P et al. Stromal cells from the adipose tissue-derived stromal vascular fraction and culture expanded adipose tissue-derived stromal/ stem cells: A joint statement of the International Federation for Adipose Therapeutics and Science (IFATS) and the International Society for Cellular Therapy (ISCT). Cytotherapy. 2013;**15**(6):641

[76] Bunnell BA et al. Adipose-derived stem cells: Isolation, expansion and differentiation. Methods. 2008;**45**(2):115-120

[77] Gnecchi M et al. Paracrine mechanisms of mesenchymal stem cells in tissue repair. Methods in Molecular Biology (Clifton, N.J.). 2016;**1416**:123

[78] Rehman JJ et al. Secretion of angiogenic and antiapoptotic factors by human adipose stromal cells. Circulation: Journal of the American Heart Association. 2004;**109**(10):1292-1298