METHOD AND APPARATUS FOR TREATMENT OF ADIPOSE TISSUE

FIELD OF THE INVENTION

The invention relates to methods and apparatuses for the reduction of adipose (fat) tissue.

LIST OF REFERENCES

The following references are brought to facilitate description of the background of the present invention, and should not be construed as limiting the scope or patentabililty of the invention:

US Patent 5,143,063

US Patent 5,158,070

US Patent Applications Nos. 2005/0154431 and 2004/0106867

US Patent 6,607,498

US Patent 6,113,558

US Patent No. 6,889,090

US Patent No. 5,871,524

US Patent No. 6,662,054

S. Gabriel, R.W. Lau, and C. Gabriel, Phys. Med. Biol. 41 (1996),pp 2251-2269

Luc Fournier and Be´la Joo´s, Physical review 67, 051908 (2003)

Alster T. S. and Tanzi, E. L., The Journal of Cosmetic and Laser Therapy. 2005; 7: 81–85

"Physical properties of tissue", by Francis A. Duck, Academic Press Ltd., 1990, p.138.

"Physical properties of tissue", by Francis A. Duck, Academic Press Ltd., 1990, p.85

Herve Isambert, Phys. Rev. Lett. 80, p3404 (1998)

K. Y. Saleh and N. B. Smith, Int. J. Hyperthermia Vol. 20, NO. 1 (February 2004), pp. 7–31.

BACKGROUND OF THE INVENTION

Reduction of subcutaneous fat layers, or adipose tissue, is an aesthetic treatment for which there is a growing demand. One method, liposuction, is a very aggressive invasive treatment requiring local or general anesthesia, and the subsequent healing process is very long and painful. Methods for non-invasive local reduction of fat are based on the delivery of electromagnetic or sound energy through the skin into the subcutaneous adipose tissue. The main challenge with non-invasive treatment of fat tissue is to transfer the energy through the outer layers of the skin, and concentrating it to the required level in the fat tissue with minimal collateral damage to the skin layers and deeper body tissues.

US Patent 5,143,063 describes a method for destruction of fat cells (adipocytes) in subcutaneous adipose tissue, in which radiant energy is focused into these cells. The radiant energy may be electromagnetic in the microwave range, or ultrasound. The major mechanism for cell destruction is the heat generated by the radiant energy. Only at the focal volume is the energy density high enough for cell destruction, while outside the focal volume the energy density is lower than the damage threshold. There is no specific selectivity for destruction of fat cells, only a geometrical selectivity created by the focusing.

US Patent 5,158,070 discloses use of ultrasound pulses of short duration that are powerful enough to tear soft tissue. Ultrasound pulses having a frequency between 3MHz to 10MHz and a pulse length of one μsec to one msec are focused in the soft tissue to effect tearing and destruction. Due to the application of short intense pulses, mechanical, and not thermal, effects are presumed to be responsible for the tissue destruction.

The following calculation provides an estimate for the peak pressure of the ultrasound wave required for this cell tearing. Assuming a plane ultrasound wave for which the cell size is much smaller then the wavelength, the local displacement U(x) is given by:

$$U(x) = U_{\max} \sin(\omega t - kx)$$

where U_{max} is the maximum displacement given by:

$$U_{\max} = \frac{V_{\max}}{\omega}$$

V_{max} is the maximum velocity, $\omega=2\pi f$, f is the frequency of the ultrasound, and k is the wave vector. For a plane wave, $\omega=kc$, where c is the sound velocity at the tissue. Taking the derivative of U with respect to x, the strains obtained:

$$\frac{dU}{dx} = -k\frac{V_{\max}}{\omega}\cos(\omega t - kx) = \frac{-V_{\max}}{c}\cos(\omega t - kx)$$

The maximal strain is V_{max}/c. The strength of a typical cell membrane has been investigated, and it was found that stretching a cell membrane by more then 2% causes it to tear, leading to cell necrosis, (Luc Fournier and Be'la Joo's, Physical review 67, 051908 (2003)). This corresponds to a strain of 0.02. Since the sound velocity in a typical soft tissue is about 1500 m/sec, for rupturing a cell membrane, V_{max} has to be over 30m/sec. For a plane wave, V=P/Z, where P is the pressure and Z is the acoustic impedance of the tissue, a typical value for Z is 1.5 MRayleigh, so that P has to be greater than 45MPa. This number corresponds to a very intense ultrasound, which can be achieved with a very high degree of focusing, and which is obtainable at frequencies in the range of a few MHz. For example, US Patent Application No. 2005/0154431, discloses adipose tissue destruction generated by HIFU (High Intensity Focused Ultrasound), with a typical frequency of 1-4MHz and a pressure of about 30MPa, close to the theoretical estimate of 45 Mpa obtained above.

This method of cell rupturing is also not selective for adipose tissue cells (adipocytes) because the adipocyte membrane is not weaker than that of other cells. Also the shape and size of the cell did not enter in the above considerations. In this respect, cell destruction by rupturing the cell membrane is similar to cell destruction by heating the cells (hyperthermia). Neither method is selective for adipocytes, and any selectivity in the method relies on geometry i.e. very strong focusing of the radiation in the adipose tissue. For both methods, a high degree of focusing yields a very small focal volume where cell destruction occurs. A typical effective focal width is a few

millimeters. Therefore, the focal volume has to be moved over the treated area. US Patent Applications Nos. 2005/0154431 and 2004/0106867 disclose such a system.

Another physical effect of focused ultrasound that can cause cell lysis, is cavitations. Cavitations are small bubbles, starting from initial small gas nucleation centers, which are driven larger by the negative pressure phase of the ultrasound wave. The rate of generation and growth of cavitations is an increasing function of the amplitude of the pressure, therefore an increasing function of the ultrasound power density. Under certain critical conditions, the bubbles collapse violently, generating in their vicinity shock waves and fluid jets that can destroy cells. In liquid environments, especially in aqueous solutions, there is evidence that collapse of cavitations causes cell necrosis and apoptosis. US patent 6,607,498 discloses focusing ultrasound energy on adipose tissue to cause cavitations and lysis of adipose tissue. US patent 6,113,558 discloses the application of focused pulsed ultrasound, which causes cavitations, for non-invasive treatment of tissues. This last patent contains a list of possible applications, which include the induction of apoptosis and necrosis, clot lysis, and cancer treatment. This patent includes a study on the generation of cavitations and on the optimization of pulse width and pulse repetition rate for maximizing the cavitations. The cavitation threshold for a non-degassed buffer solution and blood are in the range of 1000-1500W/cm^2, while for degassed fluids the threshold rises to 2000W/cm^2. The ultrasound frequency in these experiments was 750 kHz. Cavitation damage is not cell selective, and can be induced on many cell types. The cavitation threshold is quite high, and can be expected to be much higher inside adipose tissue, since most of the tissue volume is fat (lipid vacuoles). As with thermal treatment and mechanical rupturing of cells by ultrasound, also with cavitation, a high degree of focusing is required to ensure treatment of the selected tissue only (geometrical selectivity). There is another reason for the importance of focusing in cavitation treatment: Cavitations absorb ultrasound very strongly. Therefore, if cavitations are created close to the applicator, that is between the focal region and the ultrasound radiating transducer (for example at the skin), then most of the ultrasound energy will be dissipated there and will not reach the target tissue in the focal volume. To prevent this from occurring, the focusing must be sufficient to assure an intensity above the minimum value for cavitation at the focal volume, while the intensity at other tissues between the transducer and focal volume must be below the threshold for cavitation.

Besides ultrasound and microwave radiation, application of RF (Radio Frequency) energy can affect both the skin and subcutaneous layers. US Patent No. 6,889,090 discloses the application of RF energy for skin treatment. US Patent No. 5,871,524, describes application of radiant energy through the skin to an underlying subcutaneous layer or deeper soft tissue layers. The main energy source is RF. A bi-polar RF application, such as described in US Patent No. 6,889,090, is preferred over unipolar RF, since in unipolar RF currents flow through uncontrolled channels in the body, and may cause unwanted damage.

RF energy is applied to the body through two conducting electrodes applied to the skin between which an alternating voltage is driven. The RF current flows according to Ohm's law through the conducting tissues, generating heat, which can affect the tissue. The conductivity of the skin layers is an order of magnitude larger than that of fat tissue. Typical skin conductivity is about 0.4S/m and that of adipose tissue is about 0.04S/m at RF frequencies between 100kHz and 10MHz (S. Gabriel, R.W. Lau, and C. Gabriel, Phys. Med. Biol. 41 (1996), pp 2251-2269). Therefore most of the current flows through the skin layers, which is good for skin treatments, for example, hair removal and skin rejuvenation. However, it is less efficient for treatment of the deeper adipose layers.

US Patent No. 6,662,054 discloses the application of negative pressure (vacuum) to a region of the skin, so that this region protrudes out of the surrounding skin, and applying RF energy to the protrusion via electrodes. Under negative pressure, the path between the RF electrodes is longer along the skin than through the subcutaneous layers. Therefore, more RF energy is delivered into subcutaneous layers than through the skin. A commercial system based on US patent 6,662,054 has proved efficient for treatment of cellulites (TINA S. ALSTER & ELIZABETH L. TANZI, The Journal of Cosmetic and Laser Therapy. 2005; 7: 81–85). Cellulite is clinically manifested by irregular skin contours or dimpling of the skin. It is caused by excess adipose tissue retention within fibrous septae. The skin irregularity is proportional to the subcutaneous fat projected into the upper dermis.

Most of the volume of an adipocyte is occupied by a fat fluid drop, known as a lipid vacuole. The typical diameter of the cell is 50-100 μm. It tends to 100 μm in adipose tissue of obese people. Between the lipid vacuole and cell membrane, is cytoplasm. Typically the width of the cytoplasm is only a few micrometers and it is not

uniform around the lipid vacuole. It can be in the range from below 1 μm in one region of the cell and 3-5 μm in other regions.

The macroscopic physical properties of adipose tissue, mass density and sound velocity, are dominated by the material of the lipid vacuole, which occupies most of the tissue volume in mature fat cells which are the cells to be treated in reduction of the fat layer. The physical properties of the lipid vacuole fluid are thus almost identical to those of fat tissue. The density of adipose tissue is about 10% lower than that of other body tissues. According to "Physical properties of tissue", by Francis A. Duck, Academic Press Ltd., 1990, p.138, the density of adipose tissue is 916Kg/m^3, while that of body fluids and soft tissue are above 1000Kg/m^3 (i.e. above the density of water). The dermis density is about 1100Kg/m^3, while that of muscles is 1040Kg/m^3. The cytoplasm and intercellular fluid are aqueous solutions so that their density is expected to be similar to that of other body fluids and soft tissues, i.e. in the range of 1020-1040 Kg/m^3. The velocity of sound is about 1430m/sec in adipose tissue, compared to 1530 m/sec for skin, at normal body temperature. Moreover, on page 85 of the Duck reference, the slope of the sound velocity versus temperature curve for fat is completely different from that of other body fluids. For fat, sound velocity decreases with increasing temperature, dropping to 1400 m/sec at 40° C, while that of water and other body fluids rises with temperature, and is about 1520 m/sec at 40°C for water and higher for body fluids and soft tissues other than fat.

A basic model of the electrical properties of cells at the microscopic level can be found in Herve Isambert, Phys. Rev. Lett. 80, p3404 (1998). The cell membrane is a poor electrical conductor and therefore behaves essentially as a local capacitor upon the application of an electric field across the cell. The charging of the cell membrane under the application of external electric field generates a stress at these membranes, yielding strain which depends on the elastic properties of the cell, and which at increased intensity can rupture the cell membrane, a phenomena known as *"electroporation"*.

SUMMARY OF THE INVENTION

The present invention provides methods and apparatuses for the treatment of adipose (fat) tissue. As used herein, the term *"treatment of adipose tissue"* includes such procedures as fat destruction, inducing fat necrosis, inducing fat apoptosis, fat redistribution, adipocyte (fat cell) size reduction, and cellulite treatment.

The apparatuses of the invention include at least one ultrasound transducer configured to be applied to a skin surface and to radiate ultrasound energy through the skin into the subcutaneous adipose tissue. The methods of the invention include directing adipose tissue through the skin layer into the subcutaneous adipose tissue.

One embodiment of the invention is based upon a new finding that pressure gradients of ultrasound energy can lead to selective treatment of the adipose tissue cells. Without wishing to be bound by a particular theory, it is believed that the treatment or destruction of adipose tissue cells by pressure gradients generated by ultrasound energy is due to differences between the mass density of the lipid and that of the other constituents of the adipocytes. As explained below, a pressure gradient in adipose tissue capable of treating or destroying the adipose tissue cells may be generated using a moderately focused ultrasound transducer.

In another embodiment of the invention, skin and a region of the underlying adipose tissue are made to protrude out from the surrounding skin surface. Ultrasound energy is then directed to adipose tissue in the protrusion. The protrusion may be formed, for example, by applying a negative pressure (vacuum) to the skin region or by mechanical manipulation of the skin region. The apparatus of this aspect of the invention includes an applicator adapted for causing a skin region to protrude above the surrounding skin region and one or more ultrasound transducers which radiate ultrasound energy preferably into the protrusion.

In yet another embodiment of the invention, ultrasound energy and RF energy are directed into the adipose tissue. The apparatus of this aspect of the invention includes an applicator having at least one pair of RF electrodes and at least one ultrasound transducer.

The present invention provides methods and apparatus for treatment of adipocytes. One aspect of the invention is based upon a new finding that pressure gradients of ultrasound energy can lead to selective treatment of the adipose tissue cells. Without wishing to be bound by a particular theory, it is believed that the selective treatment of adipose tissue cells by pressure gradients generated by ultrasound energy is due to differences between the mass density of the lipid and that of the other constituents of the adipocytes.

When ultrasound energy is directed to a fat cell, for frequencies of less than about 1 MHz, the wavelength of the ultrasound wave is about 1.5 mm, much larger than

the fat cell dimensions, which are 50-100μm. For a plane acoustic wave propagating through the tissue having pressure amplitude P_{max}, angular frequency ω and wave vector $k=2\pi/\lambda$, where λ is the wavelength, the pressure p(x,t) is:

$$p(x,t) = P_{\max} \sin(\omega t - kx) \tag{1}$$

Neglecting viscosity, the movement of fluids can be calculated from Euler's equation:

$$\frac{\partial \vec{v}}{\partial t} + (\vec{v} \cdot \nabla)\vec{v} = -\frac{1}{\rho}\nabla p \tag{2}$$

Where v is the velocity vector, and ρ is the mass density of the fluid. For small velocities (compared to the sound velocity c) the term (v∇)v can be neglected and the velocity is proportional to the pressure gradient. For the plane wave of equation 1, since the motion is only in the x-direction:

$$\frac{\partial v}{\partial t} = -\frac{1}{\rho}\frac{\partial p}{\partial x} = \frac{P_{\max} k}{\rho}\cos(\omega t - kx) \tag{3}$$

The velocity is:

$$v(x,t) = \frac{P_{\max} k}{\rho \omega}\sin(\omega t - kx) \tag{4}$$

And the local displacement of the fluid is:

$$U(x,t) = -\frac{kP_{\max}}{\rho \omega^2}\cos(\omega t - kx) \tag{5}$$

This is the formula for a plane acoustical wave, and for such a wave ω=kc and kP_{max} is the pressure gradient.

Let ρ_{li} be the density of the fluid of the lipid vacuole, and ρ_{cy} the density of the cytoplasm fluid in an adipocyte. The respective amplitudes of the displacements can be calculated using equation (5) and substituting the corresponding densities:

$$U_{li} = \frac{kP_{\max}}{\rho_{li}\omega^2} \qquad U_{cy} = \frac{kP_{\max}}{\rho_{cy}\omega^2}$$

And the relative movement of the two fluids is given by:

$$\Delta U = U_{li} - U_{cy} = \frac{kP_{\max}}{\omega^2}\left(\frac{1}{\rho_{li}} - \frac{1}{\rho_{cy}}\right) \qquad (7)$$

Numerical example:

Taking typical values for the adipocytes, ρ_{li} =916Kg/m^3, ρ_{cy}=1020Kg/m^3, and taking P_{max}= 4MPa, $\omega=2\pi f$, f=250kHz, and c=1400m/sec, $k=\omega/c=1122m^{-1}$, the result is ΔU=0.2 μm. The physical meaning is that the cytoplasm fluid, which is a "minority" fluid in the adipose tissue, oscillates under these conditions with respect to the "majority" fluid, the lipid vacuole, with an amplitude of 0.2 μm. The pressure of P_{max}= 4MPa corresponds to the power flow density of $P^2/2Z$= 6.2MW/m^2=620W/cm^2 and to a peak pressure gradient of kP_{max} =4.5GPa/m

A relative displacement of 0.2 μm is significant at the scale of cellular dimensions. The cytoplasmic layer in the adipocytes has a thickness of few micrometers, at some regions of the cell even below 1 μm. More specifically, there are regions of the cell where over a length of 5-10 μm the width of the cytoplasm changes from below one micrometer to few micrometers. At the narrower regions, the fluid movement of the cytoplasm is damped by viscosity, while at the wider regions the cytoplasm is freer to move. Under the conditions of this example, there is a difference of displacement of about 0.2 μm over a length of 5-10 μm, which means a strain of 0.04-0.02. Since the cell membrane borders the cytoplasm, the cell membrane is also subjected to that strain, which is above the threshold for membrane rupture.

Another effect that may be associated with the above relative movement of adipocyte fluids is selective heating of the cytoplasm. The viscosity will cause some of the kinetic energy to be converted into heat. Since the cytoplasm is a minority fluid in the fat tissue and since the lipid vacuole fluid has poor heat conductance, the generated heat will selectively raise the temperature of the cytoplasm and of the cell membrane bordering it, and may lead to cell necrosis or apoptosis, directly by the local temperature rise at the membrane, or by lowering its strength at the elevated temperature.

For a non-plane wave, kP_{max} in equation 7 must be replaced by the more general pressure gradient, ∇P, in accordance with Euler's equation. It is known to use focusing of the ultrasound energy to generate very high power densities in a focal volume. It helps in two ways: first, it facilitates production of high power densities by an ultrasound transducer, and, second, it generates geometrical selectivity for the desired effect at the focal volume. However it should be noted that focusing, especially strong focusing, enhances the peak pressure substantially more than the pressure gradient. As a limiting example, a spherical transducer will generate at its center a very high peak pressure but zero pressure gradient, a manifestation of the fact that at the center the fluid is not moving. The focusing may be described physically as a superposition of plane waves. The pressure amplitude is a scalar, and at the focus the phases of the plane waves are identical, therefore the pressure at the focus is a scalar sum of the pressure amplitudes. However, the pressure gradient, and the displacement which is proportional to that gradient (by Euler's equation), are vectors, therefore their vector summed amplitude is always smaller than the sum of the magnitudes. More specifically, for strong focusing, the ultrasound radiation arrives at the focus from directions with large angular deviations, reducing the vector sum of the pressure gradient and of the fluid displacement. Therefore, according to the invention, it is preferred to limit the focusing in order to enhance the pressure gradient at the expense of the pressure amplitude at the focus, so that the selective effects on the fat cell will be obtained without the undesired effects associated with high pressure, such as cavitations.

Thus, in its first aspect, the present invention provides a method for treatment of adipose tissue in a region of subcutaneous adipose tissue comprising directing applying at least one source of ultrasound energy to a skin surface to generate a pressure gradient in the region, said pressure gradient generating relative movement between fat cells

constituents having different densities, the relative movement having sufficient intensity to cause a treatment of the fat cells.

In its second aspect, the invention provides a method for treatment of adipose tissue in a region of subcutaneous adipose tissue comprising:

a. forming a protrusion of skin and underlying adipose tissue containing the region; and

b. radiating ultrasound energy into the region.

In its third aspect, the invention provides a method for treatment of fat tissue in a region of subcutaneous adipose tissue comprising:

a. radiating ultrasound energy into the region; and

b. generating an RF electric field inside the region.

In another of its aspects, the invention provides an apparatus for treatment of adipose tissue in a region of subcutaneous adipose tissue comprising at least one source of ultrasound energy configured to direct ultrasound energy through a skin surface to generate a pressure gradient in the region, said pressure gradient generating relative movement between fat cell constituents having different densities with sufficient intensity to cause treatment of the fat cells.

In another of its aspect, the invention provides an apparatus for treatment of adipose tissue in a region of subcutaneous adipose tissue comprising:

a. a device configured to form a protrusion of skin and underlying adipose tissue containing the region; and

b. at least one ultrasound energy source configured to radiate ultrasound energy into the region.

In still another of its aspects, the invention provides an apparatus for treatment of fat tissue in a region of subcutaneous adipose tissue comprising:

a. An ultrasound energy source configured to direct ultrasound energy through a skin surface into a region of subcutaneous adipose tissue; and

b. At least two electrodes driven by an RF power source configures to generate RF field inside said region of adipose tissue.

In another of its aspects, the invention provides a method for treatment of adipose tissue in a region of subcutaneous adipose tissue comprising:

a. forming a protrusion of skin and underlying adipose tissue containing the region;

b. radiating ultrasound energy into the region; and

c. generating an RF electric field inside the adipose tissue.

In still another of its aspects, the invention provides an apparatus for treatment of adipose tissue in a region of subcutaneous adipose tissue comprising:

a. a device configured to form a protrusion of skin and underlying adipose tissue containing the region;

b. at least one ultrasound energy source configured to radiate ultrasound energy into the region; and

c. at least two RF electrodes and an RF driver configured to produce an RF electric field inside the protrusion.

BRIEF DESCRIPTION OF THE DRAWINGS

In order to understand the invention and to see how it may be carried out in practice, preferred embodiments will now be described, by way of non-limiting examples only with reference to the accompanying drawings, in which:

Fig. 1 shows the *"view angle"* of an ultrasound transducer and vector summation of pressure gradients;

Fig. 2 shows an apparatus for reduction of adipose tissue in accordance with one embodiment of the invention;

Fig. 3 shows an applicator, including an ultrasound transducer for use in the system of Fig. 1;

Figs. 4a and **4b** show pressure distribution contours generated by a flat, uniform phase ultrasound transducer;

Fig. 5 shows an applicator configured to radiate ultrasound energy into a body protrusion created by negative pressure;

Fig. 6 shows the applicator of Fig. 5 provided with a degree of freedom for the ultrasound transducer to rotate and adapt to the protrusion;

Figs. 7a and **7b** show an applicator configured to radiate ultrasound energy into a body protrusion created by mechanical manipulation of the skin;

Fig. 8 shows an applicator, including at least one ultrasound transducer and at least a pair of RF electrodes;

Fig. 9 shows an applicator including at least one ultrasound transducer and at least a pair of RF electrodes configured to provide RF and ultrasound energy into adipose tissue at a protrusion created by mechanical manipulation of the skin;

Fig. 10 shows an applicator including at least one ultrasound transducer and at least a pair of RF electrodes, configured to provide RF and ultrasound energy into the adipose tissue at a protrusion created by negative pressure (vacuum); and

Fig. 11 shows schematically an alternative arrangement of the for RF electrodes with respect to the ultrasound transducers.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS OF THE INVENTION

According to invention, based on the above considerations, an apparatus for selective destruction of fat cells will include an ultrasound transducer, which is moderately focused. Referring to Fig.1, an ultrasound transducer **21** has a focal point **22**. The view angle α of the transducer edges from the focal point correlates with the focusing in a very general way: The larger α the larger the focusing. The displacement and the pressure gradient at the focus generated by waves coming from the edges of the transducer, is the vector sum of vector **24a** and vector **24b** yielding vector **25**. The magnitude of the vector **25** is the magnitude of the vector **24a** multiplied by $2\cos(\alpha/2)$ (assuming **24a** is equal to **24b**). For $\alpha=120^\circ$ this factor is 1, compared to a factor of 2 for the scalar summation of the pressure at the same point. That is, for large α the pressure is enhanced by the focusing much more then the pressure gradient. Therefore, to obtain the selective fat reduction according to the invention, the angle α is limited. Preferred values are $\alpha<120^\circ$, more preferred $\alpha<90^\circ$.

According to the invention, based on equation 7, for selective destruction of fat cells it is preferred to radiate the ultrasound at low frequencies, preferably lower than 1MHz, more preferred below 300kHz. The numerical example above demonstrated that at 250kHz peak pressure gradient of 4.5GPa/m is expected to selectively damage fat cells. For moderate focusing this corresponds to a power flow density of about $700W/cm^2$, which is lower than the threshold for cavitation, which is preferably avoided according to the invention.

Pulsed operation is another way according to the invention for enhancing the selective effects of the ultrasound for cell destruction. Short pulses with high intensity generate high strain at the cell membranes due to the high pressure gradients, while the average power is low enough to prevent non-selective damage by excessive heating of tissues. Also, for selectively heating of cytoplasm and cell membranes by viscosity it is preferred to apply short intense pulses, since this viscosity heating effect is non-linear. Typical parameters may be: pulse length between 10 μsec and 10 msec, more preferred between 100 μsec and 1 msec.

The pulse repetition rate is preferably matched to the pulse length to generate a power duty of 1% to 10%. The average power is preferably controlled by peak power and duty, in order to control the heating of tissues. While the basic effect is non-thermal, some increase in temperature may be desired, since it reduces the strength of the cells. Preferably tissue heating above normal body temperature is kept below 44°C, a temperature known as the pain threshold. Controlled tissue heating according to the invention can be obtained from the ultrasound energy, more preferably, RF energy is applied to the treated volume as detailed below.

The pulse width and pulse repetition rates are preferably selected to be as far as possible from those optimal for cavitations at the treated tissues. As disclosed in US Patent No. 6,113,558, there is an optimal pulse length and pulse repetition frequency for generating cavitations, which are preferably to be avoided. These optimal conditions for cavitations may depend on tissue type and its conditions (such as temperature). Therefore the specific minimum cavitations conditions may require some matching to the treated site. A cavitations sensor may be included in the system to assist finding the minimum cavitations conditions. Detection of cavitations can be based on the detection of enhanced reflections at the transmitted ultrasound frequency or by the detection of ultrasound radiation at half the transmitted frequency, which is a known indication of cavitations.

The differences in sound velocities between the lipid vacuole and other fluids in the fat tissue are due to differences in compressibility. At elevated temperature, the difference increases. ("Physical properties of tissue", by Francis A. Duck, Academic Press Ltd., 1990, p.85, Fig. 4.1). For example, the sound velocity at 40° C for fat and other body fluids is 1400m/s and 1520m/s, respectively. The respective adiabatic compressibility values are $\beta=5.6\times10^{-10}$ and $\beta=4.2\times10^{-10}$. Thus, under these conditions,

the fat is more compressible than other body fluids by 30%. However, high pressures are required to exploit this. For example, a pressure of P=10MPa will generate a relative volume changes $\Delta V/V=\beta P=5.6x10^{-3}$ and $\Delta V/V=\beta P=4.2x10^{-3}$ for the lipid and cytoplasm respectively. The difference between the fluids is $1.4x10^{-3}$, which over a scale of typical cell size (50-100 micrometers) will cause a relative movement of about 0.1μm. For comparison, the mass density difference effect yielded movement of about 0.2μm at a lower pressure of 4MPa.

In accordance with one aspect of the invention, at least one ultrasound transducer configured to be applied to a skin surface, radiates ultrasound energy through the skin into the subcutaneous fat layers to effect relative movement between fat cell constituents and to cause fat cell necrosis or apoptosis. According to the invention, a flat transducer having a uniform phase over its surface is used, or a moderately focused transducer with fixed focus, or a phased transducer array, which can produce a moderate focus and can be electronically scanned inside the fat tissue to cover a larger treatment volume.

As explained above, almost all prior art high power ultrasound applications use a very high degree of focusing, to enhance the ratio between the wanted damage at the target tissue and unwanted damage at the entrance layers (between transducer and target). However, since according to the present invention the tuning is for selective damage to fat cells, moderate focusing is used. Moderate focusing can reduce unwanted cavitations effects while not reducing cell rupturing. This is attributed to the fact that cavitations depend on the pressure magnitude of the ultrasound wave (more specifically, on the negative pressure magnitude) and not on the pressure gradient.

In another of its aspects, the invention provides a method and apparatus for delivering ultrasound energy to subcutaneous adipose tissue. According to this aspect of the invention, skin and a region of the underlying adipose tissue are made to protrude out from the surrounding skin surface. Ultrasound energy is then directed to adipose tissue in the protrusion. The protrusion may be formed, for example, by applying a negative pressure (vacuum) to the skin region or by mechanical manipulation of the skin region. The apparatus of this aspect of the invention includes an applicator adapted for causing a skin region to protrude above the surrounding skin region and one or more ultrasound transducers which radiates ultrasound energy preferably into said protrusion.

Creating a protruding region of skin and underlying adipose tissue and radiating the ultrasound energy preferably parallel or close to parallel to the non-protruding skin surface, has the advantage that the radiation is preferentially directed into the fat tissue inside the protrusion while much less ultrasound energy is directed into other body tissues. This reduces the risks of unwanted damage to deep body tissues which might be much more sensitive to ultrasound energy, such as lungs, and reduces the pain which is known to be effected when high intensity ultrasound radiation heats the bones. A preferred apparatus according to the invention may include at least two ultrasound transducers with overlapping irradiated focal volumes inside the adipose tissue. The relative phases of the emitted radiation from said transducers may be controlled for maximizing the pressure gradients at selected locations inside the treated tissue.

In another of its aspects, the present invention provides a method and apparatus for treating subcutaneous adipose tissue. The method comprises directing ultrasound energy and RF energy to the adipose tissue. The apparatus of this aspect of the invention includes an applicator having at least one pair of RF electrodes and at least one ultrasound transducer. Applicant's co-pending US Patent Application 11/189,129 discloses the combination of high frequency ultrasound energy and RF energy in skin rejuvenation treatments. That application discloses generating a path of higher RF conductivity by heating of selected tissue volume by focused ultrasound, and applying RF to the body which will preferentially flow through the high conductivity path. However the situation with adipose tissue is much more complex, due to the large differences in the mechanical, electrical and thermal properties of the majority lipid vacuole fluid and the minority cytoplasm and intercellular fluids. The total electrical conductivity inside the tissue is composed from direct, Ohmic conductivity of the intercellular fluid, and the Ohmic conductivity of the fluids inside the cells in series with the capacitance of the cell membrane (which is a poor conductor). Since in mature adipose cells, most of the cell volume is filled with the poorly conducting fluid of the lipid vacuole, most of the current flows in the narrow channels of the cytoplasm and the intercellular fluid. Thus, although both RF energy and ultrasound energy are known to be poorly absorbed in fat tissue, most of the absorbed energy goes to the very thin layers of fluids between the lipid vacuoles, which occupy a very small fraction of the fat tissue volume. While on average, a relatively small amount of energy is absorbed in the adipose tissue, the specific energy transferred to the small volumes of cytoplasm and

intercellular fluid may be high. The fact that the cell membrane borders these fluids makes the energy investment in these fluids very effective for destruction of the cell membrane, followed by cell necrosis or apoptosis. Selective heating of these fluids can be achieved by exploiting the difference in the cell fluid properties, as discussed above. The RF energy and the ultrasound energy combine in these specific fluids of the fat tissue, so the desired effects are enhanced without increasing the danger of collateral damage which might be produced in other tissues, especially at the skin through which the energy is delivered, if the energy of a single type is increased to obtain the same effect. The combination of ultrasound energy and RF energy is more effective in several ways. The heating of tissue by ultrasound increases the RF conductivity, so that more energy is delivered by the RF, and the total heating reduces the cell strength. In adipose cells, these effects are concentrated mainly in the thin layers of the cytoplasm, so it is more effective for destruction of fat cells and the selectivity is enhanced by the combination. The combination of ultrasound and RF energy also increases the strain on the fat cell membrane, since both ultrasound and RF induce such strain on fat cells. The ultrasound wave generates a strain at the fat cell membranes as discussed above. The electric fields of the RF also generate strain due to charging of the membranes (see, for example, Herve Isambert, Supra). Simultaneous application of RF and ultrasound on the same tissue volume yields a combined strain. In the adipose tissue both effects concentrate at the thin cytoplasm and the adjacent membrane of the adipocytes. That combination may reduce the intensity required from each energy source, so that the risk of collateral damage may be reduced.

In a preferred embodiment of this aspect of the invention, at least one ultrasound transducer and at least two RF electrodes are applied to the protuberance. A region of skin and underlying adipose tissue to be treated is made to protrude above the surrounding skin surface. The RF energy may be applied prior to or during formation of the protuberance to pre-heat the tissue. The RF energy may be applied prior to and/or at least partially simultaneously with the ultrasound energy. When this protrusion is created, the transducers are driven to radiate ultrasound energy into the protruding tissues. RF energy is applied to the tissue via the at least two electrodes, which are either conductive for direct injection of current to the skin, or insulted by a thin layer of insulating material for capacitive coupling of energy to the tissue.

Application of RF and ultrasound energies to a protruding region of skin allows treatment of subcutaneous adipose tissue and cellulites.

Fig. 2 shows an apparatus **4** for applying ultrasound to subcutaneous adipose tissue in accordance with one embodiment of the invention. An applicator **3**, to be described in detail below, contains one or more ultrasound transducers. The applicator is adapted to be applied to the skin of an individual **5** in a region of skin and underlying adipose tissue to be treated. The applicator **3** is connected to a control unit **1** via a harness **2**. The control unit **1** includes a power source **8**. The power source **8** is connected to an ultrasound driver **6**. The control unit **1** contains a processor **9** for monitoring and controlling various functions of the system. The control unit **1** has an input device, such as a keypad **10** that allows an operator to input to the processor **9** selected values of parameters of the treatment, such as the frequency, pulse duration and intensity of the ultrasound energy to be directed to the adipose tissue.

The applicator **3** may optionally contain one or more pairs of RF electrodes in addition to the ultrasound transducers. In this case, the power supply **8** is connected to an RF generator **15** that is connected to the RF electrodes in the applicator **3** via wires in the cable **2**. When RF electrodes are included in the applicator **3**, the processor **9** may monitor the electrical impedance between electrodes and determined the temperature distribution in the vicinity of the target from the impedance measurements. The system **1** may optionally includes cooling means for cooling the skin surface during treatment. For example, the control unit may contain a refrigeration unit **12** that cools a fluid such as ethanol or water for cooling the applicator **3**. The cooled fluid flows from the refrigeration unit **12** to the applicator via a first tube in the harness **2**, and flows from the applicator **3** back to the refrigeration unit via a second tube in the harness **2**.

The control unit may also include a vacuum pump **18** for evacuating an interior chamber in the applicator **3**, in order to cause a region of the skin surface to protrude above the surround surface. The pump **18** is connected to an interior chamber of the applicator **3** by a vacuum hose in the cable **2**, as explained below.

In accordance with one aspect of the invention, the applicator **3** is configured to deliver ultrasound energy to a region of subcutaneous adipose tissue that so as to generate a pressure gradient in the region that ruptures selectively fat cells in the in the region.

Fig. 3 shows an embodiment **3a** of the applicator **3**. The applicator **3a** includes at least one ultrasound transducer **37**. The transducer is connected through a cable, preferably a coaxial cable in the harness **2** to the ultrasound driver **6** in the control unit **1**. In use, the ultrasound transducer is attached to the skin surface **27**, preferably with ultrasound gel or other ultrasound transmitting material, and generates a focal volume **33** extending around focal point **22** inside the subcutaneous adipose tissue **35**. According to one aspect of the invention, the view angle α **23** is limited to maximize the ratio of pressure gradient to pressure at the focal volume. Preferred values are $\alpha<120°$, more preferred $\alpha<90°$. The control unit **1** drives the ultrasound transducer at an intensity which produces at the focal volume pressure gradient between 0.5GPa/m to 50GPa/m, more preferred between 2GPa/m to 15GPa/m. Preferably, the ultrasound radiation is at a frequency lower than 1MHz, more preferred below 300kHz. Pulsed operation of the transducer is preferred, preferred pulse lengths being between 10 μsec and 10 msec, more preferred between 100 μsec and 1 msec. The pulse repetition rate is preferably matched to the pulse length to generate a power duty of 1% to 10%.

The ultrasound transducer of the embodiments **3a** may be flat with uniform phase over its radiating surface. This embodiment has the advantage of simplicity both of the transducer and the driving electronics. A flat, uniform phase transducer generates a pressure distribution, which has a maximum at a focal region, where the pressure can reach more than 1.5 times that on the transducer surface. Fig. 4 shows a specific example for a flat transducer with a 20x20 mm radiating area. In the diagrams of Fig. 4, the x-axis is parallel to the transducer surface while the z-axis is normal to the transducer surface. The origin is at the center of the transducer. Dimensions are in mm. Fig. 4(a) is calculated for ultrasound frequency of 180 kHz, and 4(b) for 250 kHz. The contour numbers are pressures, normalized to a unit pressure on the transducer surface. Since the focusing is very small, contours of pressure gradients at the focal region (not shown) are very close to the pressure contours. The choice of the ultrasound frequency controls the distance from the transducer face to the maxima, and which thus determines the depth of treatment. In Fig. 4(a), the region **29a** of maximum pressure has an amplitude of 1.68, and is located between z=10mm to z=20mm. For a frequency of 250kHz with the same radiating area, the maximum pressure is 1.66 and moves to a region **29b** between z=16mm and z=32mm, further from the transducer face, as shown in Fig. 4(b). It is also preferred to select the thickness of the layer between the radiating

surface and the skin so that the skin surface is at a region of minimum of radiation intensity. Human skin is typically 1.5-2.5 mm thick. Referring again to Fig. 4(a), contours of minimum pressure are at a distance of up to about 4 mm from the radiating surface. By coating the transducer face with a layer of material having acoustical impedance close to that of human tissues and having a thickness of about 4mm, a ratio of about 1.66 between the maximum pressure in the subcutaneous adipose tissue and maximum pressure at the skin is obtained.

A curved transducer and/or transducer with a lens which produces stronger fixed focusing can be applied according to the invention. Another embodiment will have the transducer **37** made as a phased array, with a multi-channel phased driver in the control unit **1**. An example of a phased array ultrasound system, with a detailed description of high intensity phased array technology as known in the art, can be found in the paper by K. Y. Saleh and N. B. Smith, Int. J. Hyperthermia Vol. 20, NO. 1 (February 2004), pp. 7–31. An apparatus based on a phased array is more complicated both in the transducer and in the driving electronics. However it has the following advantages:

a. Control of degree of focusing.
b. Control of depth and position of focal volume.
c. Possible scanning of focal volume inside a selected volume of tissue.

At least one element of the array, or any additional small transducer in the non-array embodiments, may be a sensor comprising a receiver that is tuned to half the transmitting frequency to detect generation of cavitations in the body tissue, and/or tuned to the transmitted frequency to detect enhanced reflectivity from hard body tissue or from cavitations. According to the output of this sensor, the control unit **1** varies the radiated ultrasound properties (pulse length, repetition rate and intensity) to minimize their unwanted effects. A phased array embodiment also enables positioning the focal volume away from the hard tissue and/or reducing the focusing to reduce cavitations.

The embodiment **3a** of the applicator has the advantage of simplicity, however, since focusing is limited, there is a risk that residual ultrasound energy will enter deeper into the body and hit sensitive tissue such as lungs and effect unwanted damage. Also, if this residual ultrasound energy were to hit bones, it might cause pain. To reduce these risks, the embodiments **3b** to **3g** may be used. These embodiments exploit the very high flexibility of fat tissue, and based on generating a protrusion out of the body surface and attaching at least one ultrasound transducer to that protrusion. This transducer radiates

preferably in a direction parallel to the undisturbed body surface, or at least as close as possible to that optimal angle. Under these conditions, the adipose tissue inside the protrusion is exposed preferentially, while much less radiation arrives at deeper body tissue. These embodiments can be based on mechanical manipulations and/or on application of negative pressure (vacuum) as detailed below.

Fig. 5 shows the embodiment **3b** of the applicator **3.** The applicator **3b** is shown in cross-section in Fig. 5 and includes a hollow dome **40** having an interior chamber **41**. At least one ultrasound transducer **42a** and possibly more transducers, such as **42b,** are located in the interior chamber **41**. The dome **40** is applied to the skin and a negative pressure is generated in the interior chamber **41** by pumping the air out through port **44** by the vacuum pump **18** located in the control unit **1** that is connected to the interior chamber by a vacuum hose **46** in the harness **2.** Due to the negative pressure, body tissue **45** including skin and subcutaneous tissue **35**, is sucked into volume **41**, thus protruding above the surrounding skin surface. This suction applies the skin surface onto the ultrasound transducers **42a** and **42b**. The transducers are connected through cables **48a** and **48b** in the harness **2** to the ultrasound driver **6** in the control unit **1.** The cables may include coaxial cables for driving the transducers and optionally for sending output signals from sensors located in the applicator **3b**, such as temperature sensors or ultrasound sensors, to the processor **9** in the control unit **1** for processing by the processor **9.**

The ultrasound transducers **42a** and **42b** have focal volumes **47a** and **47b** located preferably in the protruding portion of the adipose tissue layer **35**. The ultrasound transducer may be of any type described above for embodiment **3a**. A flat, uniform phase transducer, having the radiation pattern as detailed in Fig. 4, is applied with proper selection of dimensions and frequency to obtain maximum intensity inside the adipose tissue at the protrusion. Any fixed focus transducer can also be applied with the focal volume preferably at that region. According to a preferred embodiment, the transducer **42a** (and also **42b** if included) will be a phased array as described for applicator **3a**. The phased array will either focus the radiation at the optimal region of the protrusion, or scan the adipose tissue inside the protrusion. Although phased array is more complicated, it has the advantages of optimal delivery of energy into the adipose tissue at the protrusion with minimal residual energy going to other tissues.

In a preferred embodiment, at least two transducers **42a**, **42b** are used so that their volumes of maximum intensity **47a** and **47b** overlap. Preferably the phases of the transducers are controlled, and matched in a way that maximizes the ultrasound intensity in the overlapping volumes or to maximize the pressure gradients there. The transducer **42a** (and the transducer **42b** and as well as any other transducers when present) is preferably oriented in the interior chamber **41** so that the direction of ultrasound radiation from the transducer is close to being parallel to the skin surface outside the protrusion. In this orientation, penetration of the ultrasound energy to internal tissues and organs below the subcutaneous adipose layer is reduced or eliminated. Another embodiment will create this preferred direction of radiation by building a transducer which radiates at an angle to its surface. That angle can be fixed and produced by inserting a material with appropriate sound velocity in front of the transducer, or by a variable radiation angle from a phased array, controlled by unit **1**.

A pressure sensor may be included inside the interior chamber **41**. In this case, the control unit **1** may be configured to drive the ultrasound transducers **42a** and **42b** when the measured pressure is within a predetermined range. The propagation of ultrasound radiation from the transducer into the tissue can be monitored by measuring the electrical impedance of the transducer, that is, by measuring the AC voltage and current on the transducer. Variations in power transmission from the transducer are manifested by changes in the voltage-current relation on the transducer.

The radiating area of each of the transducers **42a** and **42b** may be, for example, between 5x5mm to 50x50mm, more preferably between 10x20mm to 20x40mm, depending on the volume of tissue to be treated.

Fig. 6 shows an embodiment 3c of the applicator **3** in which the transducers **42a** and **42b** are allowed a degree of freedom so that they can acquire an orientation that conforms to the skin surface in the protrusion. In the embodiment of Fig. 6, at least one ultrasound transducer, or the two ultrasound transducers **42a** and **42b** are mounted on hinges **52a** and **52b** respectively, and displaced towards the center by respective springs **55a** and **55b**. The electrical cables **48a** and, **48b** are flexible, so that the transducers are free to rotate about the hinges **52a** and **52b**. Negative pressure is created inside the interior chamber **41** as explained above with reference to Fig. 5. As the tissue is sucked into the interior chamber **41**, it pushes the transducers **42a** and **42b** against the force of springs **55a** and **55b**, thus causing them to rotate on the hinges **52a** and **52b**

against the force of the springs **55a** and **55b**. The direction of maximum acoustical radiation (beam direction) of the transducer **42a** is indicated in Fig. 6 by ray **58**, creating an angle β with the normal **57** to the non-protruding skin surface. As explained above with reference to Fig. 5, the angle β is preferably as close as possible to 90° (i.e. the radiation is close to being parallel to the non-protruding skin surface). In embodiment **3c**, the angle β depends on the properties of the tissues at the treatment site and on the controllable parameters, such as the negative pressure amplitude, its application time and the spring constants of the springs **55a** and **55b**. The closer the angle β is to 90°, the lower the amount of energy that traverses the adipose tissue **35** and enters other tissues deeper inside the body.

The ultrasound transducer(s) of embodiment **3c** can be any of those applicable to embodiment **3a** and **3b**. When a phased array is used, the phase of each element is controlled by an electronic driving circuit in the control unit **1**, so that the focal volume can be aimed easily by the electronic control of the array at a desired region inside the adipose tissue. When the transducers **42a** and **42b** in the embodiment **3c** of the applicator **3** are phased arrays, an angle encoder can be associated with each of the hinges **52a** and **52b** to determine the orientation of the transducers **42a** and **42b**. The desired focal point can then be determined according to their orientation, and the control unit **1** will phase the array to bring the focal volume to that position inside the fat tissue. The time scale of vacuum pumping is between 50 msec and 1 sec, which is also the time scale of variation of the angles of the transducers, while the focal point can be shifted within a few tens of microseconds to the desired location. Another important advantage of a phased array is the ability to scan a selected volume within the adipose tissue, by electronically controlling the phase of the array elements. The electronic scanning is fast, and can cover a large volume within the typical pumping time. Also, the degree of focusing can be controlled by the electronics.

In another embodiment, the generation of the protrusion of skin and underlying adipose tissue is done by mechanical manipulation of the skin surface. This embodiment avoids the need to vacuum system as is required when the protrusion is formed by negative pressure.

Fig. 7 shows an example of an embodiment **3d** of the applicator **3** which delivers a mechanical manipulation of a skin surface in order to generate a protruding region of skin tissue and underlying adipose tissue. The applicator **3d** includes a base element

300, which may be connected to a handle (not shown). Grooves 301 and 302 are provided inside the base element 300 in which bars 303 and 304, respectively, can move laterally. Rods 305 are 306 are attached to the bars 303 and 304, respectively. Plates 307 and 308 are connected to the lower end of the rods 305 are 306, respectively. The lower surface of these plates is preferably rough or covered with a suitable high-friction material 309 in order to enhance friction and reduce slippage over the skin. Ultrasound transducers 311 and 312 are attached to plates 307 and 308 respectively through hinges 313 and 314 respectively so as to be free to rotate about the hinges. The springs 315 and 316 displace the transducers, 311 and 312, respectively towards the skin surface 27. At the upper end of the rods 305 and 306, rods 317 and 318, respectively, are connected. The rods 317 and 318 are driven by an actuator 319.

The embodiment 3d has two ultrasound transducers, arranged symmetrically. This is by way of example only and a non-symmetrical mechanical manipulator with only one transducer or more than two transducers may be used as required in any application.

The embodiment 3d of the applicator 3 is used to create a protrusion of a skin surface as follows. The plates 309 and 310 are applied onto the skin surface 27 at a site to be treated, as shown in Fig. 7a. The actuator 319 pulls the rods 305 and 306 inwards together with the plates 307 and 308 and the transducers 311 and 312. As shown in Fig. 7b, due to the high coefficient of friction between the layer 309 and the skin surface, the body tissue 320 is pushed upwards so as to form a protrusion 330. The springs 313 and 314 are designed so that the moment they exert on the transducers 311 and 312 is low enough to allow the transducers to rotate about the hinges 313 and 314, respectively, so as to allow formation of the protrusion, while at the same time, ensuring good coupling of ultrasound energy from the transducers 311 and 312 to the skin surface 27. After the protrusion has been formed, the transducers 311 and 312 radiate ultrasound energy into the body tissue, to effect reduction of the fat in focal volumes 47a and 47b in the subcutaneous adipose tissue 35. The ultrasound transducers may be contained inside the plates 307 and 308. In this case, it is desirable to allow a degree of freedom of movement to these plates, so as to allow them to conform to the protrusion as it forms, either freely, or by forcing them to rotate simultaneously with the lateral motion.

The plates **307** and **306** and/or the transducers **311** and **312** may be curved in any desired shape in order to obtain a protrusion having a desired shape. The transducers **311** and **312** of the embodiment **3d** may be any of those applicable for the other embodiments, **3a-3c**, that is, planar transducers, fixed focus transducers or phased array transducers. If a phased array is used, in a similar way to embodiment 3c (Fig. 6), a position encoder is preferably added to hinges **313** and **314**, and the focal position electronically matched to the orientation of the transducers.

The apparatus **4**, with the applicator **3b** or **3c** or **3d**, may be configured to deliver ultrasound energy to a region of subcutaneous adipose tissue so as to generate a pressure gradient in the region that ruptures cells in the in the region. Since this effect is obtained using moderate focusing of the ultrasound radiation in a volume of subcutaneous adipose tissue to be treated, when the overlying skin surface is made to protrude above the surrounding surface, a larger power may be applied with lower risk to internal organs and tissues.

Ultrasound energy may be delivered to the skin together with RF energy; as explained above. Fig. 8 shows schematically an embodiment **3e** of the applicator **3** in which an ultrasound transducer **71** is located between two RF electrodes **72** and **73**. The transducer and RF electrodes are supported by an insulating housing **77**. Application of the applicator **3e** to the skin surface **27**, applies both the ultrasound transducer **71** and the RF electrodes **72** and **73** to the skin surface **27**, to obtain good coupling of the RF and ultrasound energies to the skin surface. An electrically conductive ultrasound conductive gel may be applied to the skin prior to the treatment. The ultrasound transducer is driven through cable **74** in the harness **2**, while cables **75** and **76** supply the RF voltage to the electrodes from the RF generator **15** in the control unit **1**.

Fig. 9 shows an embodiment **3f** of the applicator **3** in which RF electrodes have been incorporated into the embodiment **3d** of Fig. 7. For example, in Fig. 9, RF electrodes **341** and **342** are located adjacent to the transducers **311** and **312**. The RF electrodes are driven through cables **75** and **76**, which are included in harness **2** (not shown). The RF electrodes can be incorporated into the plates **307** and **308** or on the transducers **311** and **312**. In the later embodiment, a thin film of electrically conducting material having negligible ultrasound attenuation is preferably applied to each transducer face touching the skin **27**, and connected to the RF power supply **15** in control unit **1**.

Fig. 10 shows another embodiment **3g** of the applicator **3** in which a pair of RF electrodes **81** and **82** has been added to the embodiment **3b** of Fig. 5. The RF electrodes **81** and **82** are located at the sides of the dome **40**, so they can contact the skin. The RF electrodes **81** and **82** are driven by the RF driver **15** in the control unit **1** by cables **83** and **84** in the harness **2.** The electrodes **81** and **82** and the cables **83** and **84** are electrically insulated from the housing and from the ultrasound transducers. The housing **40** is preferably made of insulating material. The high conductivity contour through the skin layer **85** is longer and takes less energy than in the planar embodiment **3e** shown Fig. 8, so a higher electric field **86** is created in the deep adipose tissue. The electric field heats the minority fluids in the adipose tissue and generates strain on the adipose tissue cell membranes, as explained above. Preferably the applicators **3f** and **3g** are designed to make the regions of maximum electric field and maximum ultrasound intensity at least partially overlap within the adipose tissue, to maximize the combined effects of the RF and the ultrasound energies. A pair of RF electrodes can similarly be added to applicator **3c**.

The applicator **3g** has RF electrodes parallel to the ultrasound transducers. It is also possible according to the invention to locate the RF electrodes at other positions, which provide at least partial overlap of the RF electric field and the ultrasound radiation within the adipose tissue. Fig. 11 shows schematically another possible arrangement of the RF electrodes and the ultrasound transducers in side view (Fig. 11a), and in top view (Fig. 11b). For simplicity, Fig. 11 shows only one pair of RF electrodes **91** and **92**, and a pair of ultrasound transducers **93** and **94**.

Preferred RF parameters, for all the embodiments, are: RF frequency between 100 kHz and 50 MHz, more preferred between 500kHz and 5MHz. Applied RF voltages are between 10V peak to 1000V peak, more preferred between 30V peak to 300V peak for a distance of 10mm between electrodes, and higher voltage for greater electrode spacing. The RF electrode spacing may be between 5mm to 50mm and their length may be between 5mm to 50mm. Preferably, the ultrasound transducer covers most of the area between the electrodes. The ultrasound transducer may be flat with uniform phase where the depth of treatment is controlled by the frequency, or a fixed focus transducer or a phased array transducer with the capability of scanning the focal volume, as in embodiments **3a-3d**. Preferably, the RF energy is applied in pulses, typically between

10 μsec 500 msec, more preferred between 1 msec to 100msec. Preferably the RF and ultrasound pulses overlap at least partially.

Monitoring the contact between the RF electrodes and the body may be done by measuring the voltage across the electrodes and the current, and calculating from that the impedance between the electrodes. Based on experience with a certain electrode structure, a range of impedances can be defined that are sufficient for the application of the RF power. As in the previous embodiments, coupling of the ultrasound energy to the body can be monitored by measuring the transducer impedance.

The applicator embodiments **3b-3g** are independent of any specific physical model for the destruction of fat cells. However, it is advantageous in all embodiments to apply the ultrasound energy in a way that maximizes the selective destruction of fat cells, as was done with embodiment **3a**, namely, to exploit the unique structure of fat cells to effect relative movement between the adipose cell constituents, leading to strain and selective heating at the cell boundary, following by damage to the cell membrane which cause cell necrosis or apoptosis.

Any of the above embodiments may be adapted for delivering infra-red (IR) energy to the skin surface. Delivering of IR illumination to the skin enhances the aesthetic treatment, so that fat, cellulites and skin can be treated simultaneously. The IR illumination can be applied to skin regions not covered by the ultrasound transducer or the RF electrodes.

CLAIMS:

1. A method for treatment of adipose tissue in a region of subcutaneous adipose tissue comprising directing applying at least one source of ultrasound energy to a skin surface to generate a pressure gradient in the region, said pressure gradient generating relative movement between fat cells constituents having different densities, the relative movement having sufficient intensity to cause a treatment of the fat cells.

2. The method according to claim 1, where the pressure gradient in the fat tissue is from 0.5 GPa/m to 50 GPa/m.

3. The method according to claim 2, where the pressure gradient in the fat tissue is from 2GPa/m to 15GPa/m.

4. The method according to Claim 1 wherein the ultrasound frequency is less than 1MHz.

5. The method according to Claim 4, wherein the ultrasound frequency is less than 300 kHz.

6. The method according to Claim 1 wherein the ultrasound is pulsed.

7. The method according to Claim 6 wherein pulse length is 10 μsec to 10 msec.

8. The method according to Claim 7 wherein the pulse length is from 100 μsec to 1 msec.

9. The method according to Claim 1 wherein the ultrasound energy is delivered by an ultrasound source having view angle from the focal point of less than 120°.

10. The method according to Claim 9 wherein the ultrasound energy is delivered by an ultrasound source having view angle from the focal point of less than 90°.

11. The method according to Claim 6 where the ultrasound radiation has a pulse length and pulse repetition rate selected to minimize generation of cavitations at the body tissues.

12. The method according to Claim 1 wherein a body tissue temperature is controlled to rise to a temperature from 37° to 44° by a power duty of the ultrasound energy source.

13. The method according to Claim 1, wherein the ultrasound source is a flat transducer having a uniform radiating phase, and the depth of the region of maximum pressure gradient is controlled by the ultrasound frequency.

14. The method according to Claim 1 wherein the ultrasound energy is generated by a phased array ultrasound transducer.

15. The method according to Claim 1 further comprising forming a protrusion of skin and underlying adipose tissue containing the region and directing the ultrasound energy into the region.

16. The method according to Claim 15 wherein the protrusion is formed by applying a negative pressure to a region of the skin surface.

17. The method according to Claim 15 wherein the protrusion is formed by applying mechanical forces to a region of the skin surface.

18. The method according to Claim 15 where two or more ultrasound sources are applied, the ultrasound sources having overlapping regions of maximum ultrasound intensity inside the protruding adipose tissue.

19. The method according to Claim 18, wherein the relative phase of the ultrasound sources is controlled.

20. The method according to Claim 15, wherein the ultrasound energy is applied by a flat transducer having a uniform radiating phase, and the depth of the region of maximum intensity is controlled by the ultrasound frequency.

21. The method according to Claim 15 wherein the ultrasound is applied by a phased transducer array.

22. The method according to Claim 15 wherein the ultrasound energy is applied by a source having at least one mechanical degree of freedom to adapt to the protrusion.

23. The method according to Claim 21 wherein the radiation pattern of the phased array is dynamically matched to a source and protrusion position.

24. The method according to Claim 1 further comprising generating an RF electric field inside the adipose tissue.

25. The method according to Claim 24 wherein the application of the RF energy is at least partially simultaneous with the application of the ultrasound energy.

26. The method according to Claim 24 wherein the RF electric field has a frequency between 100 KHz and 100 MHz.

27. The method according to Claim 26 wherein the RF frequency is between 500 KHz and 5 MHz.

28. The method according to Claim 24 wherein the RF voltage is between 10V peak and 1000V peak.

29. The method according to Claim 28 wherein the RF voltage is between 30V peak and 300V peak.

30. The method according to Claim 24 further comprising monitoring an RF impedance on the RF electrodes.

31. The method according to Claim 15 further comprising generating an RF electric field inside the region.

32. The method according to Claim 1 further comprising measuring an electrical impedance of an ultrasound transducer to monitor coupling of the ultrasound energy to the body.

33. The method according to Claim 1 further comprising illuminating at least a portion of the body surface with infrared light.

34. A method for treatment of adipose tissue in a region of subcutaneous adipose tissue comprising:

a. forming a protrusion of skin and underlying adipose tissue containing the region; and

b. radiating ultrasound energy into the region.

35. The method according to Claim 34 wherein the protrusion is formed by applying a negative pressure to the skin surface.

36. The method according to Claim 34 wherein the protrusion is formed by applying mechanical forces to a region of the skin surface.

37. The method according to Claim 34 wherein the ultrasound energy is directed at an angle to the normal to the non-protruding skin surface.

38. The method according to Claim 37 wherein the angle is greater than 30°.

39. The method according to Claim 38 wherein the angle is greater than 45°.

40. The methods according to Claim 34 where two or more ultrasound sources are applied, the ultrasound sources having overlapping regions of maximum ultrasound intensity inside the protruding adipose tissue.

41. The method according to Claim 40 where the relative phase of the ultrasound sources is controlled.

42. The method according to Claim 34 wherein the ultrasound energy is applied from a flat transducer having a uniform radiating phase, and the depth of the region of maximum intensity is controlled by the ultrasound frequency.

43. The method according to Claim 34 wherein the ultrasound energy is applied from a phased array.

44. The method according to Claim 34 wherein the ultrasound energy is applied from a source having at least one mechanical degree of freedom to adapt to the protrusion.

45. The method according to Claim 43 wherein the phased array has a radiation pattern that is dynamically matched to the array and protrusion position.

46. The method according to Claim 34 wherein the ultrasound frequency is less than 1MHz.

47. The method according to Claim 46 wherein the ultrasound frequency is less than 300kHz

48. The method according to Claim 34 wherein the ultrasound is pulsed.

49. The method according to Claim 48 wherein pulse length is from 10 μsec to 10 msec.

50. The method according to Claim 49 wherein the pulse length is from 100 μsec to 1 msec.

51. The method according to Claim 35 wherein negative pressure is applied for duration between 50 msec and 1 sec.

52. The method according to Claim 51, wherein the negative pressure is applied for a duration between 100 msec and 500 msec.

53. The method according to Claim 35 wherein the ultrasound radiation starts when a predetermined negative pressure is applied to the skin surface.

54. The method according to Claim 34 further comprising measuring an electrical impedance of an ultrasound transducer to monitor coupling of the ultrasound energy to the body.

55. The method according to Claim 34 further comprising generating an RF electric field inside the adipose tissue.

56. The method according to Claim 55 wherein the application of the RF energy is at least partially simultaneous with the application of the ultrasound energy.

57. The method according to Claim 55 wherein the RF electric field has a frequency between 100 KHz and 100 MHz.

58. The method according to Claim 57 wherein the RF frequency is between 500 KHz and 5 MHz.

59. The method according to Claim 55 wherein the RF voltage is between 10V peak and 1000V peak.

60. The method according to Claim 59 wherein the RF voltage is between 30V peak and 300V peak.

61. The method according to Claim 55 further comprising monitoring an RF impedance on the RF electrodes.

62. The method according to Claim 34 further comprising illuminating at least part of the treated body surface with infrared light.

63. A method for treatment of fat tissue in a region of subcutaneous adipose tissue comprising:

a. radiating ultrasound energy into the region; and

b. generating an RF electric field inside the region.

64. The method according to Claim 63 wherein the application of the RF energy is at least partially simultaneous with the application of the ultrasound energy.

65. The method according to Claim 63 wherein the ultrasound frequency is less than 1MHz.

66. The method according to Claim 65 wherein the ultrasound frequency is less than 300kHz.

67. The method according to Claim 63 wherein the ultrasound is pulsed.

68. The method according to Claim 67 wherein pulse length is 10 μsec to 10 msec.

69. The method according to Claim 68 wherein the pulse length is from 100 μsec to 1 msec.

70. The method according to Claim 63 wherein the RF electric field has a frequency between 100 KHz and 100 MHz.

71. The method according to Claim 79 wherein the RF frequency is between 500 KHz and 5 MHz.

72. The method according to Claim 63, wherein the RF voltage is between 10V peak and 1000V peak.

73. The method according to Claim 72 wherein the RF voltage is between 30V peak and 300V peak.

74. The method according to Claim 63 wherein an RF impedance on the RF electrodes is monitored.

75. The method according to Claim 63 further comprising measuring an electrical impedance of an ultrasound transducer to monitor coupling of the ultrasound energy to the body.

76. The method according to Claim 63 further comprising illuminating at least part of the treated body surface with infrared light.

77. An apparatus for treatment of adipose tissue in a region of subcutaneous adipose tissue comprising at least one source of ultrasound energy configured to direct ultrasound energy through a skin surface to generate a pressure gradient in the region, said pressure gradient generating relative movement between fat cell constituents having different densities with sufficient intensity to cause treatment of the fat cells.

78. The apparatus according to Claim 77 where the pressure gradient at the fat tissue is from 0.5GPa/m to 50GPa/m.

79. The apparatus according to Claim 78 where the pressure gradient at the fat tissue is from 2GPa/m to 15GPa/m.

80. The apparatus according to Claim 77 wherein the ultrasound energy has a frequency less than 1MHz.

81. The apparatus according to Claim 80 wherein the ultrasound energy has a frequency less than 300kHz

82. The apparatus according to Claim 77 wherein the ultrasound energy is pulsed.

83. The apparatus according to Claim 82 wherein pulse length is 10 μsec to 10 msec.

84. The apparatus according to Claim 83 wherein the pulse length is from 100 μsec to 1 msec.

85. The apparatus according to Claim 77 wherein the ultrasound source has a view angle from the focal point less than 120°.

86. The apparatus according to Claim 85 wherein the view angle of the ultrasound source from the focal point is less than 90°.

87. The apparatus according to Claim 77 wherein the ultrasound radiation has a pulse length and pulse repetition rate selected to minimize generation of cavitations at the body tissues.

88. The apparatus according to Claim 87 further comprising a cavitations sensor and a control unit, the control unit changing the pulse length and repetition rate of the ultrasound source to minimize the output of the cavitations sensor.

89. The apparatus according to Claim 77 further comprising a control unit configured to control the pulse length or pulse repetition rate to achieve a predetermined tissue temperature.

90. The apparatus according to Claim 89 wherein the predetermined tissue temperature is from 37° to 44°.

91. The apparatus according to Claim 77 wherein the ultrasound source is a flat transducer having a uniform radiating phase, the depth of the region of maximum pressure gradient being controlled by the ultrasound frequency.

92. The apparatus according to Claim 77 wherein the ultrasound source is a phased array transducer.

93. The apparatus according to Claim 77 further comprising a device configured to form a protrusion of skin and underlying adipose tissue containing the region and ultrasound energy is directed into the region.

94. The apparatus according to Claim 93 wherein the device is configured to form a protrusion by applying a negative pressure to the skin.

95. The apparatus according to Claim 93 wherein the device is configured to form a protrusion by applying mechanical forces to a region of the skin surface.

96. The apparatus according to Claim 93 comprising two or more ultrasound sources, the ultrasound sources have overlapping regions of maximum ultrasound intensity inside the protruding adipose tissue.

97. The apparatus according to claim 96 wherein the relative phase of the ultrasound sources is controlled.

98. The apparatus according to Claim 93 wherein the ultrasound source has at least one mechanical degree of freedom to adapt to the protrusion.

99. The apparatus according to Claim 98 wherein the ultrasound source is a phased array having a radiation pattern that is dynamically matched to the source and protrusion position.

100. The apparatus according to Claim 77 further comprising at least two electrodes and an RF power source driving these electrodes to generate an RF electric field inside the adipose tissue.

101. The apparatus according to Claim 100 further comprising a controller configured to apply the RF energy at least partially simultaneous with the application of the ultrasound energy.

102. The apparatus according to Claim 100 wherein the RF electric field has a frequency between 100 KHz and 100 MHz.

103. The apparatus according to Claim 102 wherein the RF frequency is between 500 KHz and 5 MHz.

104. The apparatus according to Claim 100 wherein the RF voltage is between 10V peak and 1000V peak.

105. The apparatus according to Claim 104 wherein the RF voltage is between 30V peak and 300V peak.

106. The apparatus according to Claim 100 further comprising a device for monitoring an RF impedance on the RF electrodes.

107. The apparatus according to Claim 77 further comprising measuring an electrical impedance of an ultrasound transducer to monitor coupling of the ultrasound energy to the body.

108. The apparatus according to Claim 77 further comprising a source of infrared light for illuminating at least part of the treated body surface with infrared light.

109. An apparatus for treatment of adipose tissue in a region of subcutaneous adipose tissue comprising:

a. a device configured to form a protrusion of skin and underlying adipose tissue containing the region; and

b. at least one ultrasound energy source configured to radiate ultrasound energy into the region.

110. The apparatus according to Claim 109 wherein the device is configured to form a protrusion by applying a negative pressure to the skin surface.

111. The apparatus according to Claim 109 wherein the device is configured to form the protrusion by applying a mechanical forces on the skin surface.

112. The apparatus according to Claim 109 wherein the ultrasound energy is directed at an angle to the normal to the non-protruding skin surface.

113. The apparatus according to Claim 112 wherein the angle to the normal is greater than 30°.

114. The apparatus according to Claim 113 wherein the angle is greater than 45°.

115. The apparatus according to Claim 109 including two or more ultrasound sources, the ultrasound sources having overlapping regions of maximum ultrasound intensity inside the protruding adipose tissue.

116. The apparatus according to Claim 115 wherein the relative phase of the ultrasound sources is controlled.

117. The apparatus according to Claim 109 wherein the ultrasound source is a flat transducer having a uniform radiating phase, and the depth of the region of maximum intensity is controlled by the ultrasound frequency.

118. The apparatus according to Claim 109 wherein the ultrasound source is a phased array transducer.

119. The apparatus according to Claim 109, wherein the ultrasound source has at least one mechanical degree of freedom to adapt to the protrusion.

120. The apparatus according to Claim 119 wherein where the ultrasound source is a phased array having a selectable radiation pattern to dynamically match the source and protrusion position.

121. The apparatus according to Claim 109 configured to generate ultrasound energy having a frequency less than 1MHz.

122. The apparatus according to Claim 121 configured to generate ultrasound having a frequency less than 300 kHz.

123. The apparatus according to Claim 109 configured to apply pulsed ultrasound energy.

124. The apparatus according to Claim 123 configured to apply pulsed ultrasound energy having a pulse length from 10 μsec to 10 msec.

125. The apparatus according to Claim 124 configured to apply pulsed ultrasound energy having a pulse length from from 100 μsec to 1 msec.

126. The apparatus according to Claim 123 configured to apply ultrasound radiation having a pulse length and pulse repetition rate selected to minimize generation of cavitations in the body tissues.

127. The apparatus according to Claim 109 further comprising a cavitations sensor and a control unit, the control unit being configured to determine the pulse length and repetition rate of the ultrasound source to minimize the output of the cavitations sensor.

128. The apparatus according to Claim 110 configured to apply negative pressure to a skin surface for a duration between 50 msec and 1 sec.

129. The apparatus according to Claim 128 configured to apply negative pressure for a duration between 100 msec and 500 msec.

130. The apparatus according to Claim 110 configured to apply the ultrasound radiation when a predetermined negative pressure is achieved on the skin surface.

131. The apparatus according to Claim 109 further configured to measure an electrical impedance of an ultrasound transducer array to monitor coupling of the ultrasound energy to the skin.

132. The apparatus according to Claim 109 further comprising at least two RF electrodes and an RF driver configured to produce an RF electric field inside the protrusion.

133. The apparatus according to Claim 132 further comprising a controller configured to apply the RF energy at least partially simultaneous with the application of the ultrasound energy.

134. The apparatus according to Claim 132 wherein the RF electric field has a frequency between 100 KHz and 100 MHz.

135. The apparatus according to Claim 134 wherein the RF frequency is between 500 KHz and 5 MHz.

136. The apparatus according to Claim 132 wherein the RF voltage is between 10V peak and 1000V peak.

137. The apparatus according to Claim 136 wherein the RF voltage is between 30V peak and 300V peak.

138. The apparatus according to Claim 132 further comprising a device for monitoring an RF impedance on the RF electrodes.

139. The apparatus according to Claim 110 further comprising:

a. a dome shaped applicator having an interior volume containing the one or more ultrasound transducers; and

b. a vacuum pump for generating a negative pressure in the interior chamber when the dome is applied to a skin surface.

140. The apparatus according to Claim 111 comprising a device for mechanically manipulating the skin, the device comprising, at least two plates adapted for contacting a skin surface, the plates being movable from a first configuration in which the plates are spaced apart by a first distance and a second configuration in which the plates are spaced apart by a second distance, the second distance being less than the first distance, the protrusion being formed when the plates are applied to a skin surface and moved from the first configuration to the second configuration.

141. The apparatus according to Claim 140 further comprising an actuator for moving the plates from the first configuration to the second configuration.

142. The apparatus according to Claim 140 further comprising means for applying the ultrasound transducer arrays to the protrusion.

143. The apparatus according to Claim 140 wherein at least one ultrasound transducer array is included in one of the plates.

144. The apparatus according to Claim 140 wherein the ultrasound transducer has at least one degree of freedom to move with respect to said plates.

145. The apparatus according to Claim 140 further comprising at least two RF electrodes and an RF driver configured to produce an RF electric field inside the protrusion.

146. The apparatus according to Claim 145 further comprising a controller configured to apply the RF energy at least partially simultaneous with the application of the ultrasound energy.

147. The apparatus according to Claim 109 further comprising a source of infrared light for illuminating at least part of the treated body surface with infrared light.

148. An apparatus for treatment of fat tissue in a region of subcutaneous adipose tissue comprising:

a. An ultrasound energy source configured to direct ultrasound energy through a skin surface into a region of subcutaneous adipose tissue; and

b. At least two electrodes driven by an RF power source configures to generate RF field inside said region of adipose tissue.

149. The apparatus according to Claim 148 further comprising a controller configured to apply the RF energy at least partially simultaneous with the application of the ultrasound energy.

150. The apparatus according to Claim 148 wherein the RF electric field has a frequency between 100 KHz and 100 MHz.

151. The apparatus according to Claim 150 wherein the RF frequency is between 500 KHz and 5 MHz.

152. The apparatus according to Claim 148 wherein the RF voltage is between 10V peak and 1000V peak.

153. The apparatus according to Claim 152 wherein the RF voltage is between 30V peak and 300V peak.

154. The apparatus according to Claim 148 further comprising a device for monitoring an RF impedance on the RF electrodes.

155. The apparatus according to Claim 148 further comprising measuring an electrical impedance of an ultrasound transducer to monitor coupling of the ultrasound energy to the body.

156. The apparatus according to Claim 148 configured to deliver pulsed ultrasound energy.

157. The apparatus according to Claim 156 wherein ultrasound pulse length is 10 μsec to 10 msec.

158. The apparatus according to Claim 157 wherein the ultrasound pulse length is from 100 μsec to 1 msec.

159. The apparatus according to Claim 148 wherein the ultrasound energy has a frequency less than 1MHz.

160. The apparatus according to Claim 159 wherein the ultrasound energy has a frequency less than 300kHz

161. The apparatus according to Claim 148 further comprising a source of infra-red light configured to illuminate at least part of the treated body surface.

162. A method for treatment of adipose tissue in a region of subcutaneous adipose tissue comprising:

a. forming a protrusion of skin and underlying adipose tissue containing the region;

b. radiating ultrasound energy into the region; and

c. generating an RF electric field inside the adipose tissue.

163. An apparatus for treatment of adipose tissue in a region of subcutaneous adipose tissue comprising:

a. a device configured to form a protrusion of skin and underlying adipose tissue containing the region;

b. at least one ultrasound energy source configured to radiate ultrasound energy into the region; and

c. at least two RF electrodes and an RF driver configured to produce an RF electric field inside the protrusion.