

# Effects of Carboxytherapy on Metabolic Health: A Narrative Review

## *Efectos de la Carboxiterapia en la salud metabólica: revisión narrativa*

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### ABSTRACT

Carboxytherapy is a medical technique that uses carbon dioxide for therapeutic purposes. This review aimed to evaluate the scientific evidence regarding the effects of carboxytherapy on metabolic health. The applications of carboxytherapy encompass several areas of medicine. Evidence indicates that carbon dioxide is not only an important regulator of blood pH, but also modulates gene expression, influences growth factors, and stimulates the production of endothelial progenitor cells. These effects are reflected in the increased microcirculation observed in the skin (where collagen production is stimulated), in subcutaneous adipose tissue (where lipolysis and tissue reduction have been documented), in muscle (where mitochondrial biogenesis and muscle fiber differentiation are promoted), and in bone (where reparative processes are stimulated). The activation of microcirculation is mediated by the upregulation of vascular endothelial growth factor expression. Despite the evidence presented, further research is needed on the application of carboxytherapy across different fields of medicine.

**Keywords:** carbon dioxide, carboxytherapy, CO<sub>2</sub>, CO<sub>2</sub> therapy.

### RESUMEN

La carboxiterapia es una técnica médica que utiliza el dióxido de carbono con fines terapéuticos. El objetivo de esta revisión fue evaluar la evidencia científica sobre los efectos de la carboxiterapia en la salud metabólica. Las aplicaciones de carboxiterapia abarcan varias áreas de la medicina. La evidencia muestra que el dióxido de carbono no sólo es un importante regulador del pH en la sangre, sino que también regula la expresión de genes, factores de crecimiento y estimula la producción de células endoteliales progenitoras. Estos hechos se ven reflejados en el incremento de la microcirculación en piel (donde se estimula producción de colágeno), en el tejido celular subcutáneo (en el que se ha evidenciado lipólisis y reducción del mismo), en el músculo (en el que estimula la biogénesis mitocondrial y la diferenciación de fibras musculares) y hueso



(en el que estimula su reparación). La activación de la microcirculación está mediada por el incremento de la expresión del factor de crecimiento de endotelio vascular. Pese a la evidencia mostrada, se necesitan más estudios de investigación de carboxiterapia aplicada en los distintos campos de la medicina.

**Palabras clave:** CO<sub>2</sub>, dióxido de carbono, carboxiterapia, terapia con CO<sub>2</sub>.

## INTRODUCTION

Carboxytherapy is a medical technique that uses carbon dioxide for therapeutic purposes. The term carboxytherapy, coined by Dr. Parassoni in 1995 during the 16th National Congress of Aesthetic Medicine in Rome (Brandi, 2022), refers to the percutaneous application of carbon dioxide through subcutaneous or intradermal gas injection. Other methods of administering carbon dioxide also exist, such as using the gas dissolved in water or incorporated into gels (Hartmann *et al.*, 1989 and Oe *et al.*, 2011).

The modern history of carboxytherapy began in France with the first experiments in the 1920s, which demonstrated the safety of subcutaneous CO<sub>2</sub> injections. In the 1930s, at the Royat Institute in Clermont-Ferrand, therapeutic applications of carbon dioxide were introduced using thermal waters to treat circulatory disorders. In 1946, the Cardiovascular Research Institute was established at the same site, one of Europe's first centers dedicated to treating cardiovascular and circulatory conditions using CO<sub>2</sub> dissolved in water. The research conducted there laid the foundations for contemporary carboxytherapy (Brandi, 2022). Initially, the medical use of carbon dioxide was indicated for two conditions: peripheral arterial disease and Raynaud's syndrome (Fabry *et al.*, 2006). Subsequent research identified its physiological effects—vasodilation, wound healing, and pain relief—supporting its therapeutic use in pathologies such as erectile dysfunction,

scleroderma, and rheumatologic disorders like arthritis and fibromyalgia (Body, 2014).

Currently, one of the most widely studied and applied uses of carboxytherapy is in the treatment of chronic wounds, with significant clinical outcomes (Prazeres *et al.*, 2025). Nonetheless, carboxytherapy has a broad range of potential applications across various branches of medicine. In dermatology, for instance, it has been successfully used for skin rejuvenation, stretch marks, infraorbital hyperpigmentation, lymphedema, alopecia, morphea, psoriasis, and vitiligo (Bagherani *et al.*, 2023). In plastic surgery, it is applied for body contouring and skin grafts; in pain therapy, for conditions such as epicondylitis, cervicalgia, and tendinitis; in gynecology, for vaginal dryness, vaginal rejuvenation, and dysmenorrhea; and in endocrinology, as an adjunct treatment for localized adiposity and weight reduction, among others (Shtroblia *et al.*, 2023).

The objective of this review was to evaluate the scientific evidence regarding the effects of carboxytherapy on metabolic health.

## MATERIALS AND METHODS

A narrative search was conducted across the PubMed, PMC, and Google Scholar databases, using various combinations of the terms “carboxytherapy,” “carbon dioxide therapy,” “carboxyterapia,” “carbon dioxide,” “CO<sub>2</sub>,” “CO<sub>2</sub> therapy,”

and “transcutaneous CO<sub>2</sub>.” The search specifically focused on the physiological effects pertaining to vasodilation, wound healing, and pain relief in relation to pathologies including erectile dysfunction, scleroderma, and rheumatological conditions. Relevant articles addressing this subject were extracted, their abstracts were systematically reviewed, and the most pertinent articles for this review were identified

## RESULTS AND DISCUSSION

### Carbon Dioxide in Biological Systems

Carbon dioxide is perpetually generated within the body and is involved in a multitude of physiological functions. A portion of this gas is expelled into the alveoli and subsequently eliminated from the body via the process of ventilation. Carbon dioxide exhibits a high diffusion capacity through tissues and cellular membranes, with its diffusion rates at rest significantly exceeding those of oxygen (400 to 450 ml/min/mmHg for CO<sub>2</sub> compared to 21 ml/min/mmHg for O<sub>2</sub>). Elevated concentrations of carbon dioxide induce the Bohr effect, wherein the oxygen-hemoglobin (O<sub>2</sub>:Hb) dissociation curve shifts to the right in response to increased concentrations of carbon dioxide and hydrogen ions within the bloodstream. This physiological response facilitates the release of oxygen from hemoglobin into the tissues. Furthermore, carbon dioxide is integral to the regulation of pH levels. When dissolved in water, carbon dioxide reacts to form carbonic acid (H<sub>2</sub>CO<sub>3</sub>), which subsequently dissociates into bicarbonate (HCO<sub>3</sub><sup>-</sup>) and hydrogen ions (H<sup>+</sup>). The equilibrium established between bicarbonate and carbonic acid is crucial for the maintenance of pH balance in blood and tissues (Hall *et al.*, 2011).

Research conducted in Europe since the early twentieth century has demonstrated that carbon dioxide can induce vasodilation in skin exposed to carbonated water (Diji & Greenfield, 1960; Hartmann *et al.*, 1989). Subsequently, a study examined the effects of immersion in CO<sub>2</sub>-enriched water on angiogenesis within ischemic limbs in murine models. The findings revealed a substantial enhancement in blood perfusion, collateral vessel formation, and capillary density. Increases in vascular endothelial growth factor (VEGF) levels, activation of nitric oxide (NO) synthesis, and mobilization of endothelial progenitor cells were noted. These results suggest that CO<sub>2</sub> therapy can facilitate neovascularization through the activation of growth factors (Irie *et al.*, 2005). Additionally, another investigation indicated that the transcutaneous delivery of CO<sub>2</sub> dissolved in water to patients suffering from diabetes mellitus and obliterative atherosclerosis resulted in a significant elevation in VEGF levels and CD34+CD33+ endothelial progenitor cells, thereby promoting angiogenesis and enhancing blood circulation in the lower extremities, culminating in a reduction of symptoms such as numbness and edema (Saito & Nonomura, 2006).

A variety of cellular sensors capable of detecting minor fluctuations in carbon dioxide concentrations have recently been identified. Through these sensors, carbon dioxide has been observed to activate or inhibit diverse functions, contingent upon its concentration and the duration of exposure (Cummins *et al.*, 2014; Galganska *et al.*, 2021). One particular study demonstrated that carbon dioxide exerts a notable anti-inflammatory effect, modulating extracellular signal-regulated kinases

1 and 2 (ERK1/2) activity in cultured endothelial cells in conditions of elevated CO<sub>2</sub> concentration. However, the effect of carbon dioxide on ERK1/2 activity is concentration-dependent (Galganska *et al.*, 2021). Carbon dioxide has also been associated with a reduction in reactive oxygen species levels and an increase in the presence of antioxidant substances (Bolevich *et al.*, 2016; Dogliotti *et al.*, 2011). Additionally, evidence suggests that carbon dioxide may influence insulin resistance through the inactivation of ERK1/2 and the p38 protein, which regulates various cellular functions and is implicated in inflammatory processes. Such applications may prove beneficial in enhancing insulin sensitivity and promoting the healing of diabetic wounds (Galganska *et al.*, 2023).

### Effects of Carboxytherapy on the Skin

In recent years, carboxytherapy has been regarded as an effective and safe tool for rejuvenation treatments, as subcutaneous administration of CO<sub>2</sub> has been shown to promote wound healing, reduce scar tissue, and enhance collagen renewal—making it a valuable procedure for achieving a wide range of aesthetic benefits. Several studies have demonstrated that the vasodilatory effect of carbon dioxide in the skin enhances microcirculation and oxygen supply, contributing to the aforementioned benefits (Diji & Greenfield, 1960; Minamiyama & Yamamoto, 2010).

An experimental study with histological analysis in rodents demonstrated that subcutaneous and intradermal injections of carbon dioxide increased collagen turnover compared with controls, and that intradermal injections achieved a greater density of collagen bundles (Ferreira *et al.*, 2008). Subsequently, a quasi-experimental study involving nine female volunteers who re-

ceived a single session of carboxytherapy in the infraumbilical region revealed, through histological analysis, a significant increase in collagen synthesis (Oliveira *et al.*, 2020).

A randomized, double-blind clinical trial confirmed the effectiveness of carbon dioxide application in promoting the healing of chronic wounds in diabetic patients. After 20 CO<sub>2</sub> therapy sessions over four weeks, 20 out of 30 wounds achieved complete healing, whereas in the control group, which received 20 placebo sessions with air, none of the wounds healed completely (Macura *et al.*, 2020). A four-year retrospective study evaluated the effects of transcutaneous carbon dioxide application in 86 patients with chronic wounds. The results showed clinical improvement in wound granulation, as well as a reduction in secretions and odor within the first week of treatment (Wollina *et al.*, 2004).

Another study examined the effects of carboxytherapy on venous insufficiency wounds in rats, comparing three groups: a control group, a group treated with silver sulfadiazine, and a group treated with carboxytherapy. The findings demonstrated that carboxytherapy reduced inflammation, improved fibronectin production, and resulted in more organized wound healing compared with the other groups (Brochado *et al.*, 2019). Carboxytherapy has also proven to be safe and effective in reducing recent facial scars, improving skin appearance (Arellano, 2013).

A recent clinical trial comparing the effects of carboxytherapy alone versus in combination with antioxidant and regenerative acids found that while carboxytherapy alone improved skin hydration and elasticity around the eyes, these effects were more pronounced when combined with

lactobionic, ferulic, and ascorbic acids. The combined therapy exhibited greater improvements in skin firmness and biomechanics, suggesting a synergistic relationship between carboxytherapy and these acids (Kołodziejczak *et al.*, 2025).

### Effects of Carboxytherapy on Subcutaneous Adipose Tissue

Over twenty years ago, a publication reported the effects of carboxytherapy on subcutaneous adipose tissue (SAT). Dr. Cesare Brandi and his research team conducted a study involving 48 women with localized fat deposits in the abdomen, thighs, and/or knees, who received subcutaneous carbon dioxide injections. The researchers evaluated microcirculation using laser Doppler imaging and measured tissue oxygen concentration, along with performing biopsies on treated areas before and after treatment. Their findings revealed a significant reduction in the volume of treated areas, increased microcirculation, elevated transcutaneous oxygen pressure, and, under microscopic examination, adipose tissue rupture with the release of triglycerides into intercellular spaces, along with adipocytes showing membrane fracture lines (Brandi *et al.*, 2001).

Another clinical trial, which included a histomorphological study of adipocytes through computed cytometry in 15 female volunteers who received six carboxytherapy sessions on the abdomen, demonstrated a significant reduction in adipocyte count in the abdominal wall, as well as morphological changes in adipocyte area, diameter, perimeter, length, and width following subcutaneous CO<sub>2</sub> administration (Costa *et al.*, 2011).

While studies have confirmed a reduction in subcutaneous fat tissue, the un-

derlying mechanism remains under investigation. Initially, it was hypothesized that the mechanical effect of gas infusion caused adipocyte rupture and subsequent lipolysis (Balik *et al.*, 2011). However, evidence now points toward a metabolic mechanism mediated by vascular endothelial growth factor (VEGF). An experimental study in mice comparing air versus CO<sub>2</sub> injections demonstrated that CO<sub>2</sub> administration (but not air) led to a reduction in adipocyte size within adipose tissue. Additionally, CO<sub>2</sub>-treated fat tissue showed markedly increased expression of the VEGF-1 and FGF-1 (fibroblast growth factor 1) genes, promoting the formation of new blood vessels within the interstitial spaces of treated adipose tissue.

Interestingly, CO<sub>2</sub> administration also increased the expression of the \*Ucp1\* gene by 1.7-fold—this gene encodes a thermogenic protein known as an uncoupling protein. Together with a decrease in lipogenic gene expression, these findings strongly support the hypothesis that carboxytherapy reduces subcutaneous adipose tissue through a **metabolic effect**, rather than by the **mechanical action** of the gas (Park *et al.*, 2018).

Furthermore, evidence suggests that carboxytherapy may contribute to improvements in metabolic parameters such as waist circumference, body mass index, triglyceride levels, and blood pressure when combined with a low-fat diet and high-intensity interval training (HIIT) (Ahmad *et al.*, 2022).

### Effects of Carboxytherapy on the Muscle

A research team from Kobe University in Japan revealed through a clinical trial that transcutaneous application of carbon dioxide produces effects comparable to

those of physical exercise, as it stimulates the expression of genes such as \*PGC-1 $\alpha$ \* (Peroxisome Proliferator-Activated Receptor Gamma Coactivator-1 Alpha), \*Sirt-1\* (Sirtuin-1), and \*VEGF\*, while also increasing mitochondrial number and promoting muscle fiber transformation (Oe *et al.*, 2011).

Akahane *et al.* (2017) investigated whether transcutaneous CO<sub>2</sub> application could enhance muscle injury recovery in rats. Muscle damage was induced in the tibialis anterior muscle using bupivacaine injections, and the rats were randomly assigned to either a treated group receiving transcutaneous CO<sub>2</sub> or an untreated control group. The results showed that CO<sub>2</sub> treatment accelerated the repair of injured muscle fibers. In addition, higher expression levels of genes and proteins associated with muscle protein synthesis were observed, along with greater capillary density in the CO<sub>2</sub>-treated group. The study concluded that transcutaneous CO<sub>2</sub> application may accelerate muscle recovery after injury in rats.

The effects of transcutaneous CO<sub>2</sub> on muscle fatigue recovery were also demonstrated in a study involving 15 healthy male volunteers. Muscle fatigue was induced through 300 maximal eccentric contractions of the quadriceps, followed by transcutaneous CO<sub>2</sub> application on the thigh. Parameters such as muscle strength, physical performance (assessed by a single-leg long jump), delayed onset muscle soreness (DOMS) using a visual analog scale, and muscle ATP and ADP concentrations were measured. The results indicated that CO<sub>2</sub> application accelerated the recovery of muscle strength and physical function, reduced DOMS, decreased ADP concentration, and increased ATP levels in

muscle tissue. This ATP synthesis may be related to the accelerated muscle recovery observed (Sakai *et al.*, 2012)

### Effects of Carboxytherapy on Bone

Carboxytherapy is a medical technique with multiple applications, and its metabolic effects (Figure 1) are supported by scientific evidence. Following its use for skin regeneration, the reduction of subcutaneous fat is among its most sought-after treatments. This localized fat reduction is associated with the lipolytic effect of carboxytherapy, demonstrated by the release of triglycerides following CO<sub>2</sub> administration (Brandi *et al.*, 2001). However, this mechanical lipolysis alone does not fully explain adipose tissue reduction, as obese and insulin-resistant patients often exhibit increased basal lipolysis associated with lipoinflammation (Engin, 2017).

Carboxytherapy stimulates microcirculation in subcutaneous adipose tissue (SAT) and improves tissue oxygenation—an effect mediated by the release of \*VEGF-1\* and \*FGF-1\*. Additionally, carbon dioxide has been shown to reduce reactive oxygen species (ROS) and stimulate the production of antioxidant compounds (Dogliotti *et al.*, 2011). These mechanisms may contribute to its fat-reducing effect. Furthermore, as previously discussed, inhibition of adipogenesis and upregulation of the thermogenic gene \*Ucp1\* are key factors in fat reduction (Park *et al.*, 2018).

Moreover, the potential effect of CO<sub>2</sub> on improving insulin resistance reinforces its metabolic impact on subcutaneous adipose tissue. At the muscular level, CO<sub>2</sub> can activate mitochondrial biogenesis (Oe *et al.*, 2011), and these activated mitochondria are responsible for initiating

$\beta$ -oxidation of fatty acids released from adipose tissue to be used as an energy source.

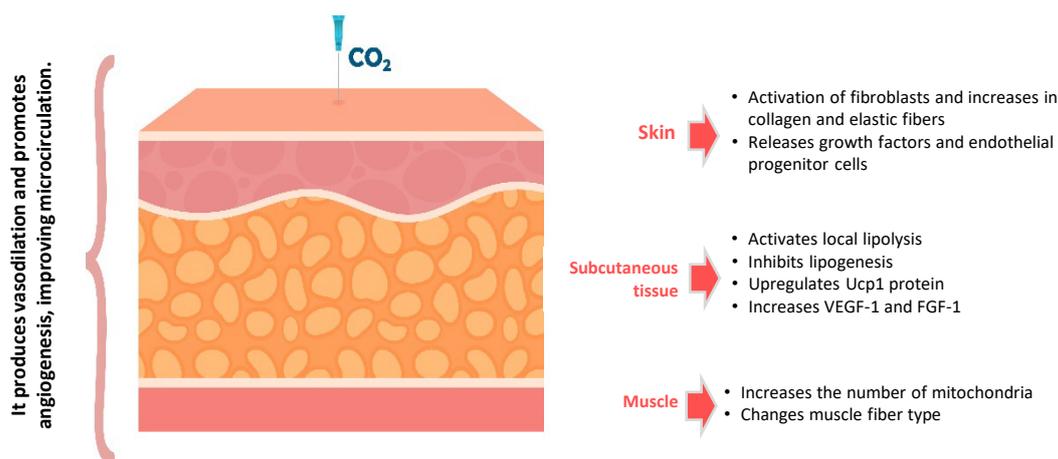
This process completes the full cycle following carboxytherapy treatment for localized adiposity:

1. Activation of microcirculation in the area encompassing gas diffusion, from the skin to the muscle tissue.
2. Enhanced lipolysis in subcutaneous adipose tissue (under non-hypoxic conditions due to the Bohr effect improving oxygenation), accompanied by reduced inflammation in adipose tissue.
3. Transport of free fatty acids through activated microcirculation from the adipose tissue to muscle, where CO<sub>2</sub> stimulates the

release of \*PGC-1 $\alpha$ \* and \*Sirt-1\*, activating mitochondrial biogenesis and  $\beta$ -oxidation of fatty acids.

The energy produced through this process manifests as heat, an effect reported in a clinical study (Abramo *et al.*, 2009). Although this temperature increase was initially attributed to vasodilation, it may also result from the metabolic process described above, as clinical practice has shown that the treated area remains warm even after the procedure concludes.

The use of carboxytherapy for muscular and bone injuries is still under investigation and development, yet the current evidence suggests highly promising therapeutic potential.



**Figure 1.** Metabolic effects of carboxytherapy application (original illustration, iCDT001-25). Ucp1: uncoupling protein and thermogenic gene; VEGF-1: vascular endothelial growth factor 1; FGF-1: fibroblast growth factor 1.1.

## CONCLUSIONS

Carboxytherapy is a medical technique with multiple applications in medicine, whose scope and benefits extend from the skin to bone tissue, sharing a common mechanism: the activation of microcirculation through the stimulation of growth factors and endothelial progenitor cells. Its

most widespread uses are in skin regeneration and the reduction of subcutaneous fat tissue. Its application in muscular and bone tissues shows great promise; however, further research across all medical fields is needed to fully understand its potential and optimize its therapeutic applications.

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- Arellano-Salazar, Martha P.: Conceptualization, methodology, writing and project administration; review and editing.

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