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Low Back Pain: Oxygen-Ozone and Ultrasound in Paravertebral Approach

Malatesta Manuela[1] & Polo Mauro[2*]

[1]*Department of Neuroscience, Biomedicine and Movement Sciences, University of Verona, Verona, Italy*
[2]*SSD Pain Therapy and Palliative Care, AULSS n. Marca Trevigiana, Montebelluna, (TV), Italy*

[*]Corresponding author: Polo Mauro, SSD Pain Therapy and Palliative Care, AULSS n. Marca Trevigiana, Montebelluna, (TV), Italy.

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Abstract

Background: *Low back pain (LBP) is a common disorder, with high repercussion in quality of life and a significant economic burden.*

Etiology is multifactorial and diagnosis focused on triggering causes. First line therapy usually starts with conservative approaches.

As minimally invasive technique, percutaneous oxygen-ozone injections, due to its analgesic and anti-inflammatory effect, represent an integrative treatment.

Objective: *Aim of this literature review is to explore the possible role and utility of ultrasound performing paravertebral oxygen-ozone therapy out of clinical settings.*

Results: *Imaging-guided procedures compared with anatomical landmarks techniques, showed better therapeutic performance with higher impact on pain reduction and lower age-related variability. The anatomical view reduces the risk, improves safety and efficacy.*

Conclusions: *Systematic reviews and meta-analyses in the literature justify ozone use in pain medicine. Evidence is low mainly for the lack of studies with adequate and consistent methodologies.*

Keywords: Ultrasound, Oxygen, Low Back Pain (LBP), Paravertebral

Introduction

Low back pain is anatomically defined as extending from the 12th rib to the iliac crest. Often Low Back Pain coexists and is conflated with buttock pain, the buttock region is anatomically distinct and comprises a region from the iliac crest to the gluteal folds.

Low back pain covers a spectrum of different types of pain (eg, nociceptive, neuropathic and nociplastic, or non-specific) that frequently overlap. The elements comprising the lumbar spine (eg, soft tissue, vertebrae, zygapophyseal and sacroiliac joints, intervertebral discs, and neurovascular structures) are prone to different stressors, and each of these, alone or in combination, can contribute to low back pain [1].

Low back pain represents the leading cause of worldwide productivity loss as measured in years and the top cause of years lived with disability in 126 countries [2].

People with physically demanding jobs, physical and mental comorbidities, smokers, and obese individuals are at greatest risk of reporting low back pain. Disabling low back pain is over-represented among people with low socioeconomic status. Most people with new episodes of low back pain recover quickly; however, recurrence is common and in a small proportion of people, low back pain becomes persistent and disabling [3]. Initial high pain intensity, psychological distress, and accompanying pain at multiple body sites increases the risk of persistent disabling low back pain. Increasing evidence shows that central pain-modulating mechanisms and pain cognitions have important roles in the development of persistent disabling low back pain. Cost, health-care use, and disability from low back pain vary substantially between countries and are influenced by local culture and social systems, as well as by beliefs about cause and effect [3].

Low back pain (LBP) is a common health problem among adults of working age population, and its prevalence or incidence in-

creases with increasing in age. The prevalence and incidence of LBP ranged from 1.4 to 20.0% and 0.024–7.0%, respectively [4]. Peak prevalence from 28% to 42% in people between 40 years and 69 years and up to 80% of the population presents mild to severe LBP at some point in life. This condition is usually self-limiting, but often becomes chronic [5].

Despite several peer-reviewed published studies on the prevalence or incidence of LBP, there is little consensus regarding its epidemiology and its risk factors [4].

Globally recognized as an important health and socioeconomic challenge, approximately two thirds of the economic costs from LBP stem from indirect costs (reduce performance at work, difficult to deal with domestic chores, caregiving, engaging in recreational activities, struggles with relationships, depression and anxiety) [1].

It is important to understand that pain is distinct from nociception and includes not just A delta fiber and C fiber activation, but also context-dependent emotional, cognitive, and behavioral elements [6]. This could partly explain the poor correlation with pathology and symptoms, and why interventions that have no effect on degenerative processes, can have profound effects on pain and quality of life, whereas interventions that address pathology (eg, surgery) often do not provide benefit. This was eloquently described by Melzack and Casey in their landmark classification of pain into sensory-discriminative, affective-motivational and cognitive-evaluative components [7]. its forms the basis for a multimodal, precision medicine approach to low back pain and is a foundation for the biopsychosocial model [8].

Studies carried out on Ozone in the last three decades underlines the unique capacity of Ozone Therapy to reactivate the innate antioxidant system to regulate the oxidative stress typical of chronic inflammatory diseases. Pain pathways and control systems of algesic signals after ozone administration are well described. In 2015 Prof. Bocci (Department of Biotechnology, Chemistry and Pharmacy, University of Siena), published a review paper that elucidate the biochemical, molecular, immunological, and pharmaceutical mechanisms of action of ozone [9].

The conclusion of this paper was in favors for the full insertion of ozone therapy into pharmaceutical sciences, rather than as either an alternative or an esoteric approach.

Over the years, infiltrative oxygen-ozone therapy has shown clinical benefits in several musculoskeletal disorders.

The development and implementation of ultrasound in clinical practice, allows real time non-invasive imaging, easily available that could be useful in oxygen-ozone therapeutic practices to improve safety and accuracy of treatment. Finally, may be an added value to optimize clinical outcomes [10].

Through a literature review, this master thesis aims to evaluate the application of ultrasound to ozone therapy as regards the treatment of LBP for the paravertebral approach. We have focused on procedural and technical aspects. The correct evaluation of outcomes is influenced by numerous biases as: multifactorial causes and risk factors associate to chronicity, the lack of homogeneous criteria to define acute or chronic pain, study design and statistical sample size, scales used to measure endpoints [11]. Regardless the taxonomic aspects, about 80-90% of LBP cases is represented by nonspecific low back pain with a diagnosis made with exclusion of other causes [12, 13]. More and more evidences show how the thoracolumbar fascia is involved with nonspecific low back pain. A dysfunction of the myofascial tissue that is not tightly contiguous with the symptomatic area is then suggested to be taken into consideration among the causes of nonspecific low back-pain.

Low Back Pain

Definition

Low Back Pain covers a spectrum of different types of pain: nociceptive (mechanical), neuropathic (radicular), mixed pain and nociplastic (caused by amplification of pain in the CNS). Anatomically defined as extending from the 12th rib to the iliac crest with or without radiate pain to lower limbs. Often coexists and is conflated with buttock pain (from iliac crest to gluteal folds).1 Up to 84 percent of adults have low back pain at some time in their lives. Patients who continue to have back pain beyond the acute period (four weeks) have subacute back pain (lasting between 4 and 12 weeks) and may go on to develop chronic back pain (persists for ≥12 weeks) [14]. Radicular pain is most associated with herniated nucleus pulposus and spinal stenosis, further stratified by location as central, foraminal, or involving the lateral recesses. Infrequently, other conditions, can cause radicular pain (eg, herpes zoster and metastatic cancer). The presence of a herniated nucleus pulposus does not always result in pain. A systematic reports prevalence rates in asymptomatic individuals ranging from 29% in 20-year old's to 43% in 80-year old's [15]. In another systematic review authors found that spontaneous regression occurred in more than 90% of sequestered discs, 70% of herniated discs, and more than 40% of protruded disc [16]. Spinal stenosis is an anatomically progressive condition and a direct consequence of age-related degenerative processes. Not everyone with narrowing of the spinal canal will have radicular pain. In one review, the range of spinal stenosis in asymptomatic individuals ranged with a median of 11% [17]. In the "Framingham Study" was found a prevalence of 22.5% for relative stenosis (lumbar spinal canal diameter <= 12mm) and 7.3% for absolute stenosis (lumbar spinal canal diameter <= 10 mm) [18]. Nociplastic pain is correlate with central sensitization and represent a cause of non-specific low back pain although it can also accompany mechanical and neuropathic pain. Many patients seen in primary care (>85 percent) have non-specific low back pain, this mean in the absence of a specific underlying condition that can be reliably identified. Many of these patients may have musculoskeletal pain and most of them improves within a few weeks [14].

Pathogenetic Factors

Multifactorial causes and risk factors contribute to pathogenesis of low back pain. Lumbar spine is made by different structures that include muscles, fascia, ligaments, tendons, facet joints, neurovascular elements, vertebrae, and intervertebral discs. All structures are susceptible to biochemical, degenerative, and traumatic stressors, (Fig. 1) according to a variable dependent on posture and movement.

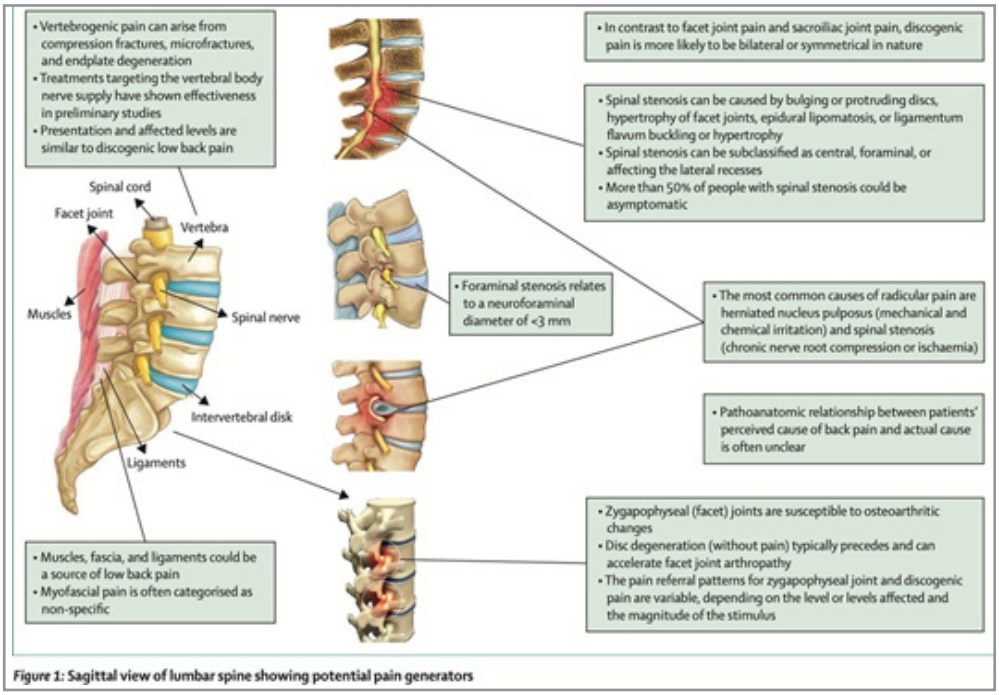


Figure 1: Sagittal view of lumbar spine showing potential pain generators

Discogenic Pain

The discs, which are 70-80% aqueous, are composed of an outer anulus fibrosus and inner nucleus pulposus. Intervertebral discs play the role to absorb shock and preserve spinal movements distributing axial and torsional forces. During healing, neovascularization occurs, and minute sensory nerves can penetrate the disrupted anulus and nucleus pulposus, leading to mechanical and chemical sensitization.

Although MRI is highly sensitive for detecting disc pathology, a systematic review found conflicting evidence that endplate signal changes were associated with low back pain and activity limitations. Another systematic review found only a modest correlation between disc space narrowing and low back pain in 26 107 patients. Like other sources of mechanical pain, discogenic pain can extend into the upper and occasionally lower legs in a non-dermatomal pattern [19, 20].

Radicular Pain

Low back pain that extends to the leg, usually below the knee (radicular pain), can result from mechanical nerve root compression and chemical irritation from various inflammatory mediators that leak out of degenerated discs. Unlike referred pain from joints, muscles, and discs, the pain typically radiates in a dermatomal distribution. Herniated nucleus pulposus is the most common cause of radicular pain, although after 60 years of age, spinal stenosis is the leading cause.

Spinal Stenosis

Spinal stenosis is most common at the L4-L5 level and can result from facet joint and ligamentum flavum hypertrophy, congenitally short pedicles, and spondylolisthesis [21]. Spinal stenosis can cause chronic mechanical compression resulting in axonal injury or nerve root ischemia. Both herniated nucleus pulposus and spinal stenosis are radiological diagnoses, but not all people with stenosis and herniations have pain.

From a radiological perspective, absolute central lumbar stenosis refers to anteroposterior spinal canal diameter smaller than 10 mm, whereas foraminal stenosis relates to a neuroforaminal diameter smaller than 3 mm. Spinal stenosis often coexists with other conditions (eg, hypertrophied facet joints causing foraminal narrowing) including herniated disc, with one study reporting a 23% co- prevalence rate [22]. Most herniated discs are substantially degenerated and the causes of spinal stenosis can also cause axial pain, most, but not all, cases of lumbar radicular pain co-occur with back pain.

Facet Arthropathy

Facet joints (ie, zygapophyseal joints) that connect adjacent vertebrae always play a role in limiting spine movements, but their role in load bearing becomes prominent as discs age and degenerate. These joints are also prone to degenerative changes, most commonly osteoarthritis [23]. Referred lumbar facet joint pain has a variable presentation; upper lumbar levels are associated with non-dermatomal pain projecting into the hip, flank, and lateral aspects of the upper thigh, which contrasts with pain felt in the lateral or posterior aspects of the thigh observed with the lower levels. The most affected L4–L5 and L5–S1 zygapophyseal joints can sometimes produce pseudo radicular symptoms extending into the lower leg.

Myofascial Pain

Muscles, fascia, and ligaments can also be pain generators. Muscles that can potentially contribute to low back pain include deep intrinsic (eg, multifidus or rotators) and the more superficial longissimus, spinalis, and iliocostalis muscles, collectively referred to as erector spinae muscles. Back muscles are integral to normal spine stiffness and function, and chronic low back pain could be paradoxically associated with both atrophy and increased myoelectric activity, Muscle pathology represents an underappreciated source of low back pain, often mis- diagnosed as non-specific, and frequently arises consequent to other primary pathology. Myofascial pain might result from overuse, acute

stretch injuries or tears, and diffuse or localized (eg, trigger points) muscle spasm.

Sacroiliac Joint Pain

The sacroiliac joint consists of an extensive network of ligaments both dorsally and ventrally, and a joint capsule in the anterior, lower-third of the sacroiliac junction. Although sacroiliac joint pain most frequently presents in the buttocks, over two-thirds of individuals will have lumbar pain; in approximately 50% of cases, the pain radiates to the leg, sometimes below the knee [24]. Nociceptors are present in ligaments and fibrous capsule and both could be a source of pain. Intra-articular pathology is more common in older people, whereas younger individuals with prominent tenderness and a traumatic cause are more likely to have extra-articular pathology.

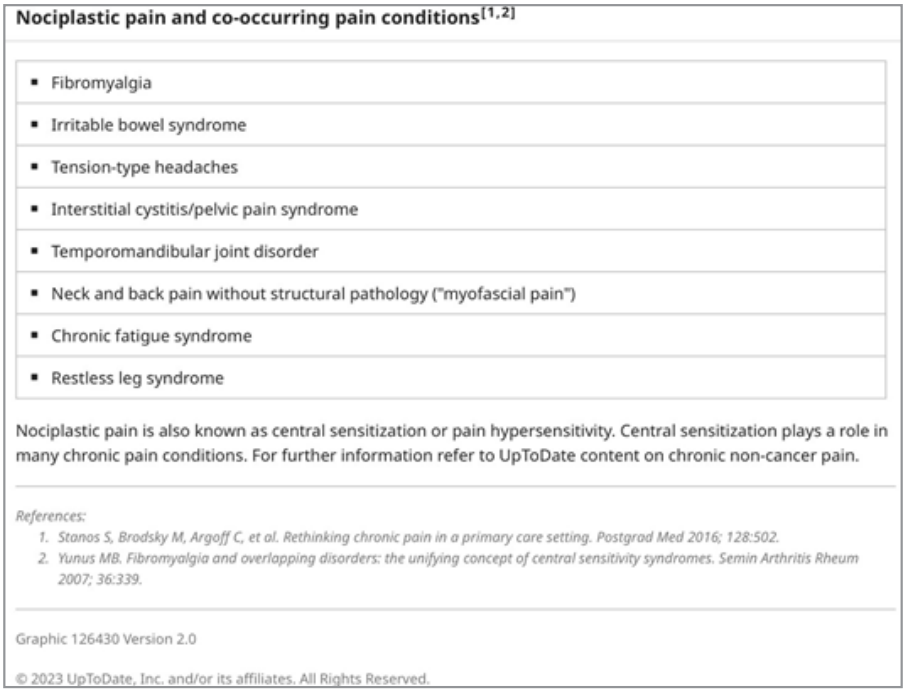
Spondyloarthropathies

Spondyloarthropathy refers to a family of inflammatory rheumatic diseases that includes ankylosing spondylitis and psoriatic arthritis. These systemic conditions typically include multiple joints, with ankylosing spondylitis and axial spondylarthritis. Axial spondylarthritis (axSpA) encompasses both radiographic and non-radiographic axSpA. It is a chronic inflammatory disease with a predilection for involving the axial skeleton. The most common presenting symptoms are chronic back pain and spinal stiffness, but peripheral and extra- musculoskeletal manifestations occur also frequently. The diagnosis of axSpA relies on the recognition of a clinical pattern of the disease, based on clinical, laboratory and imaging features. In addition to facet and sacroiliac joint arthritis, other spinal manifestations include enthesitis and auto fusion. The prevalence of ankylosing spondylitis (AS) have been reported in Europe as between 0.12 and 1.0 percent. The prevalence for the whole group of axial SpA has been estimated to be two to three times higher than that of AS alone. Back pain that is chronic and almost constant is one of the cornerstones of axial SpA. Patients with axial SpA typically have chronic low back pain of more than three months' duration; in most axial SpA patients, the onset of low back pain is before age 45. However, chronic low back pain of all causes, especially mechanical or nonspecific back pain, is common, with a prevalence estimated at about 20 percent of the general population only a small minority of these individuals has axial SpA.

Nociplastic Pain

The term "nociplastic" pain was coined to recognize that many patients have pain that is not fully described by tissue injury (nociceptive pain) or nerve injury or disease (neuropathic pain) [25]. Nociplastic pain is defined by the IASP as pain that results from altered nociception, without evidence of actual or threatened tissue damage that causes activation of peripheral nociceptors, and without evidence for disease or a lesion causing the pain. The term "nociplastic," pain may not yet be commonly used clinically; it conveys similar concepts to terms such as "central sensitization," and "centralization," when characterizing pain. Nociplastic pain can accompany both nociceptive pain and neuropathic pain.

Altered pain sensory processing and impaired central pain modulation appear to play a prominent role in many chronic pain conditions.



Nociplastic pain and co-occurring pain conditions[1,2]

- Fibromyalgia
- Irritable bowel syndrome
- Tension-type headaches
- Interstitial cystitis/pelvic pain syndrome
- Temporomandibular joint disorder
- Neck and back pain without structural pathology ("myofascial pain")
- Chronic fatigue syndrome
- Restless leg syndrome

Nociplastic pain is also known as central sensitization or pain hypersensitivity. Central sensitization plays a role in many chronic pain conditions. For further information refer to UpToDate content on chronic non-cancer pain.

References:

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2. *Yunus MB. Fibromyalgia and overlapping disorders: the unifying concept of central sensitivity syndromes. Semin Arthritis Rheum 2007; 36:339.*

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Figure 2: "Evaluation of Chronic non-Cancer Pain in Adults" From UpToDate Nov 08, 2022

These conditions are characterized by the neurophysiologic phenomenon of "central sensitization," or "nociplasticity," which may also play a role in the transformation of acute pain into chronic pain.

Several patient factors increase the risk of developing chronic pain, including genetics, patient fears and expectations, prior poor pain-related treatment outcomes, psychiatric and behavioral co-occurring conditions, adverse social issues, older age, and long-term opioid use.

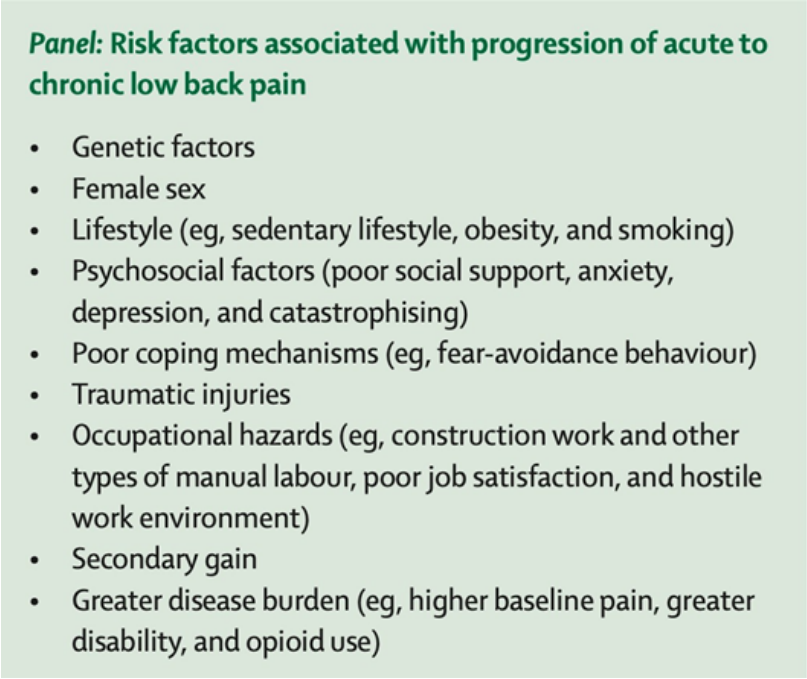

Figure 3: Acute to Chronic Risk Factors. From Lancet, Vol. 398, July3, 2021

A 2020 review raised the possibility of an increase in chronic pain following the COVID-19 pandemic, since acute infections can trigger chronic pain syndromes and patients may report pain as part of post-COVID-19 syndrome [26, 27].

Genetic Factors

The genetic determinants of low back pain have received increased attention in the past decade and could someday be part of precision medicine algorithms. Carvalho- E-Silva and colleagues found that heritability contributed 26% to lifetime prevalence of low back pain, 36% for functional limitations, and 25% to pain intensity in 1598 twins [28]. A systematic review of studies involving twins showed that the effects of heritability accounted between 21% and 67% of back pain burden [27, 29]. One question raised by genetic studies is how individually identified genes contribute to low back pain (eg, through pain perception, accelerated spondylosis, predisposing psychopathology, lifestyle, and response to treatments), and the role that epigenetics plays.

Diagnostical Aspects and Clinical Evaluation

Despite the fact most cases of low back pain are non-specific or resolve without formal diagnosis, large part of guidelines recommend history taking and physical examination to identify specific entities. More than half of the guidelines favored triaging patients into three categories: non-specific low back pain, specific mechanical low back pain, or radicular pain; the remainder were against separate classification [1]. The recommendations were uniform against the endorsement of imaging in patients with non-specific low back pain; however, more than half of the guidelines recommended imaging in patients with so-called red flags and yellow flags during evaluation, which can lead to interventions that can prevent persistent disability (Fig.4).

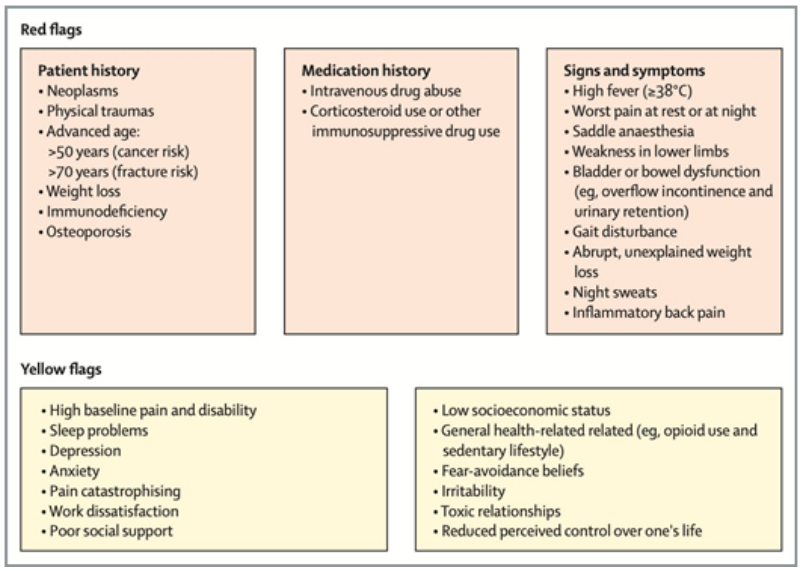

Figure 4: Red and Yellow Flags for LBP From The Lancet2021;398 Page84

A large retrospective review showed that presence of red flags such as fracture, metastases, and infection increased the probability of identifying serious spinal pathology, although a negative response to red flag surveillance did not lower the probability of a red flag diagnosis. Other flags associated with prognosis for low back pain include orange (psychiatric symptoms), yellow (beliefs, appraisals, judgements, emotional responses, and pain- related behavior), blue (relationship between work and health), and black (system or contextual obstacles) flags. Concerning imaging numerous guidelines have been published for low back pain. The result is high rates of use but also high prevalence rates for abnormalities in asymptomatic volunteers (most people have disc degeneration by age 40 years). Poor correlation between symptoms and pathology [30]. For acute low back pain, red flags, including severe or progressive neurological deficits, warrant imaging. For chronic low back pain, routine imaging is not recommended, although it could be considered on a case-by-case basis, particularly when findings are likely to affect care (e.g., referral for surgery). Plain films can be considered when evaluating for spinal instability (flexion and extension), spondylolisthesis, or screening for scoliosis. In patients who are candidates for MRI but have contraindications, CT scans have greater than 90% sensitivity for detecting most lumbar pathology [31].

Clinical Considerations

LBP frequently recognize variable and multi-factorial etiology.

Annular tears and disc disruption often anticipate an intervertebral disc herniation and typically manifests as low back pain eventually associated with lower limb radiate pain for nerve root irritation. This pain usually resolves over several weeks in patients without neurological deficits but might persist in others. A prospective cohort study highlighted recurrent pain at 6 months in more than half of patients with LBP (with or without sciatica). The extent of disc herniation does not correlate well with severity of pain [1].

Clinical presentation and diagnostic evaluation of low back pain are shown below in Fig. 5.

	Risk factors	Onset of condition	Clinical presentation*	Physical findings†	Diagnostic imaging
Mechanical pain					
Intervertebral disc[34,37,38]	Advanced age, but patients typically younger than those with facetogenic or sacroiliac joint pain; repetitive or acute trauma	Insidious	Low back pain and leg pain; pain worse with sitting	Midline tenderness; reduced range of motion, especially bending forward; no focal neurological findings	Plain films to evaluate disc height; MRI to detect annular tears, fissures, or high intensity zones; imaging not routinely needed
Facet joint[39]	Osteoarthritis; spondylolisthesis	Insidious	Axial low back pain; referred pain to hip, flank, or upper thigh	Paraspinal greater than midline tenderness; reduced back range of motion; no focal neurological findings	CT is gold standard for bone pathology, with SPECT scans showing correlation with facet block results; imaging not routinely needed
Muscles, fascia, and ligaments[38]	Strenuous activity; repetitive or abrupt movements (eg, coughing, sneezing)	Acute or insidious	Axial low back pain; occasional referred pain to the posterior thigh	Muscle guarding, spasm, oedema, or atrophy; reduced back range of motion; no focal neurological findings	Ultrasound; imaging not routinely needed
Sacroiliac joint[37,39]	Bimodal age distribution; trauma; pregnancy; previous surgery; spondyloarthropathy; advanced age; leg length discrepancy	Often follows trauma in the form of axial loading and abrupt rotation	Buttock pain; low back pain frequently radiating into the leg or groin; sitting or rising from sitting can worsen it	Tenderness near posterior superior iliac spine; pain worse with rising from sitting; no focal neurological findings	X-rays and radionuclide bone scans have low sensitivity; CT most sensitive for bone involvement; MRI might detect active inflammation and soft tissue pathology
Vertebral body	Advanced age, history of trauma	Insidious	Low back pain, with or without upper leg pain	Midline tenderness, pain worsened by activities, no focal neurological findings	Plain films to evaluate for acute compression fracture, MRI to detect endplate signal changes and acuity (eg, active inflammation)
Radicular pain					
Herniated disc[37,38,39]	Peak frequency age 30–50 years, more frequent in men with heavy lifting; trauma; lifestyle habits (smoking, obesity); symptoms can be caused by inflammatory cytokine release from discs	Acute or insidious	Low back pain or leg pain, or both	Straight leg raising test; crossed straight leg raising test; dermatomal pain location; diminished reflexes depending on nerve root involvement; lower extremity muscle weakness depending on nerve root involvement; weakness can be pain-induced or neurological	MRI for nerve root compromise (sensitivity 0·25; specificity 0·92); CT or CT myelography to differentiate soft tissue changes from osteophytes; imaging recommended for serious or progressive neurological deficits
Spinal stenosis[39–41]	Advanced age, hypertrophy of facet joints and ligamentum flavum; degenerative spondylolisthesis; disc bulging; congenital (eg, short pedicles)	Insidious	Low back pain and leg pain; wide-based gait; neurological weakness	At least three to five findings from patient history and examination (age >48 years, leg pain greater than back pain, bilateral symptoms, pain with walking or standing, pain alleviation with sitting); improved walking ability with the spine flexed forward; pain relief with bending; muscle weakness and diminished reflexes depending on nerve root involvement	MRI for soft tissues and measuring spinal canal diameter; CT can assess osseous diameter of spinal canal in axial views, but is less sensitive than MRI; plain x-rays used to evaluate spinal instability (flexion or extension)

SPECT=single photon emission tomography. *There is considerable overlap within radicular causes (eg, spinal stenosis and herniated disc) and within mechanical causes (eg, sacroiliac joint pain, facet joint pain, and degenerative discs), with frequent co-occurrence. †Historical and physical findings tend to be more sensitive than specific, and are not pathognomonic.

Figure 5: Clinical Presentation and Diagnostic Evaluation in LBP -From. Lancet 2021;398: Page 83

Patients with lumbar stenosis can report LBP and leg pain aggravated by walking and alleviated by bending forward. These symptoms are referred to as intermittent neurogenic claudication, well distinguished from vascular claudication. (Fig. 6) Straight leg raising test, in spinal stenosis, is less reliable [32].

Comparison of symptoms in neurogenic and vascular claudication

Symptoms	Neurogenic	Vascular
Quality	Pain/numbness/tingling/weakness	Pain/cramping/tightness
Increased with walking	Yes	Yes
Relieved walking flexed with a cart	Yes	No
Relieved standing erect	No	Yes
Relieved sitting/lying	Within minutes	Immediate
Increased walking uphill/upstairs	No/less	Yes
Increased walking downhill	Yes/more	Yes
Increased biking/back flexed	No	Yes
Increased biking/back extended	Yes	Yes

Graphic 80902 Version 3.0

Figure 6: Comparison of symptoms in neurogenic and vascular claudication. From UpToDate

Sciatica is a specific type of LBP referring to pain radiating down the buttock and leg along the path of sciatic nerve, usually compressed in the setting of spine osteoarthritis. LBP and sciatica affect hundred million people worldwide, regardless of age, sex, occupation and lifestyle with approximately 80% of the population experiencing LBP during their lives. Economic and social impact of LBP is therefore impressive, with higher incidence of depression and isolation commonly described in affected people [33].

Treatment should generally begin with conservative methods (i.e., oral medications, physical therapy, exercise, occupational modifications); second-line treatments include a wide spectrum of minimally invasive techniques, before resorting to a more invasive surgical approach (mandatory in case of neurological deficit, progressive foot droop and paralyzing sciatica). Among minimally invasive techniques, percutaneous oxygen-ozone (O2-O3) gaseous mixture injections are one of the most common and effective procedures adopted in case of conservative approach failure.

LBP and the Rationale of Oxygen-Ozone Therapy

Ozone (O3), or trioxygen, is an inorganic gas, an allotrope of oxygen with lower stability than the diatomic di-oxygen (O2). Ozone immediately reacts as soon as it is dissolved in biological water (physiological saline, plasma, lymph, urine, interstitial fluid), where atomic oxygen act as a very reactive species. Ozone reacts with both present antioxidants and polyunsaturated fatty acids (PUFAs). The lipid peroxidation by ozone leads to the simultaneous formation of both ROS and LOPs. One of the ROS is hydrogen peroxide, which is a non-radical oxidant able to act as an ozone messenger responsible for eliciting several biological and therapeutic effects. The transitory formation of O2•- (anion superoxide), •OH (hydroxyl radical), and 1O2 (singlet oxygen) is possible, but their small amounts are irrelevant [9]. Although ROS have a lifetime of less than a second, they can damage crucial cell components and therefore their generation must be precisely controlled to achieve a biological effect without any damage. LOP production follows the peroxidation of PUFAs. They are intrinsically toxic and must be generated in very low concentrations. Antioxidants, such as ascorbic and uric acids; compounds with-SH groups, such as reduced glutathione as well as albumin are molecules that react and neutralize ozone. On the other hand, if the ozone amount is excessive, carbohydrates, enzymes, DNA, and RNA can also be oxidized and broken down. In conclusion, it must be clear that a correct ozonation process either carried out in blood, or intradiscally and intramuscularly, should represent an acute but tolerable oxidative stress giving the hermetic-type response of the interacting biological system [9].

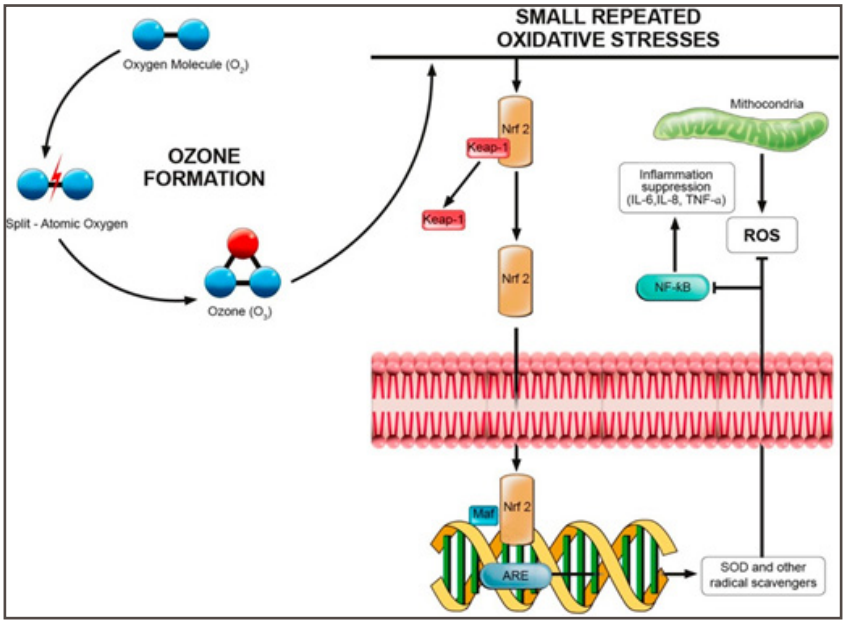

Figure 7: Pathways in Inflammation and Oxidative stress. From: Biomolecules2021,11,356

Medical ozone is an analgesic, antiseptic, anti-inflammatory, immune-modulating gas, active on pro-inflammatory cytokines, prostaglandins, and bradykinins synthesis. Upregulation of endogenous antioxidant systems and the activation of pathways suppressing inflammatory processes are the main mechanisms of action of Oxygen-Ozone Therapy. Combined with low-concentration oxygen-ozone is used for intramuscular/paravertebral and/or intradiscal injections. The main indication is represented by LBP with or without radicular pain in absence of motor deficits, refractory to 4–6 weeks conservative therapy [33]. The therapeutic mechanism of action can be identified in its high reactivity: once injected, ozone is able to produce a short and self-limiting oxidant action with a consequent increase in the biological antioxidant cell response. In this light, ozone acts as a prodrug, activating endogenous mediators that cause a change in cellular metabolism. Its benefits range from the inhibition of inflammation and correction of ischemia and venous stasis, to the reflex induction of endorphin release, as well as the promotion of antinociceptive analgesic effects Oxygen-ozone therapy (OOT) might exert its action in reducing LBP with a coupled mechanical and anti-inflammatory effect. The direct effect (mechanical) consists in the lysis of the proteoglycans composing the disc's nucleus pulposus, which results in the release of water molecules and the subsequent cell degeneration of the matrix,

which is then replaced by fibrous tissue, leading to a reduced disc volume. The indirect effect (anti-inflammatory) is realized by altering the breakdown of arachidonic acid to inflammatory prostaglandins. As result, by reducing the inflammatory components, there is a subsequent decrease in pain. Furthermore, the stimulation of fibroblastic activity can promote the repair process by stimulating collagen deposition. This is the rationale behind O2-O3 injections in the paravertebral muscles corresponding to the metamer of the herniated disc.

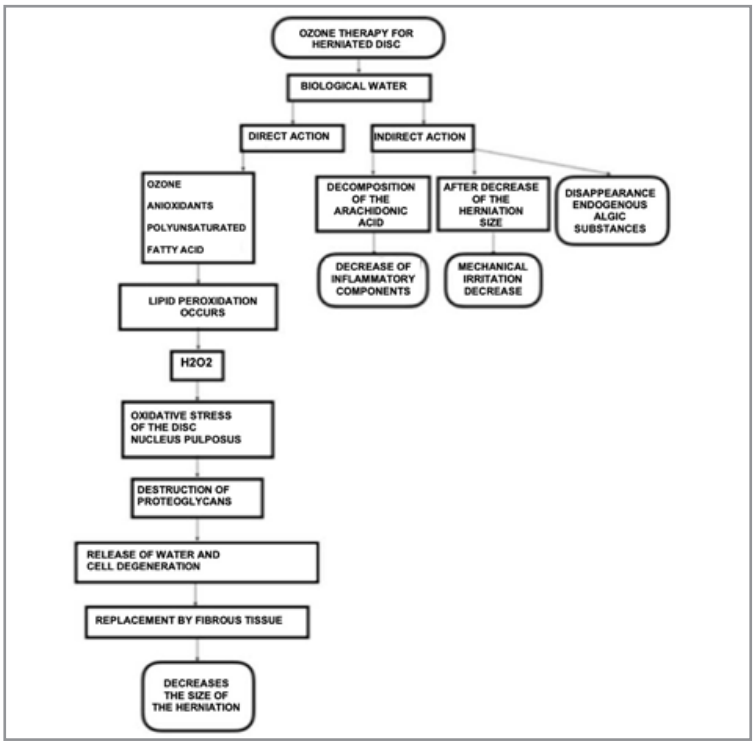

Figure 8: From Rev. Assoc. Med. Bras. 2020;66(8): Page1149

Paravertebral: The "Indirect Approach"

The paravertebral muscles are used as a route for infiltration of O2-O3 and consists in one or several (up to four) injections of 5–10 mL of oxygen-ozone gaseous mixture per site. It has been defined as "chemical acupuncture" because both the needle and gas injection have a role in eliciting a complex series of chemical and neurological reactions leading to the disappearance of pain in the majority (positive responses in 70–80% of cases) of patients with low spinal pain [9].

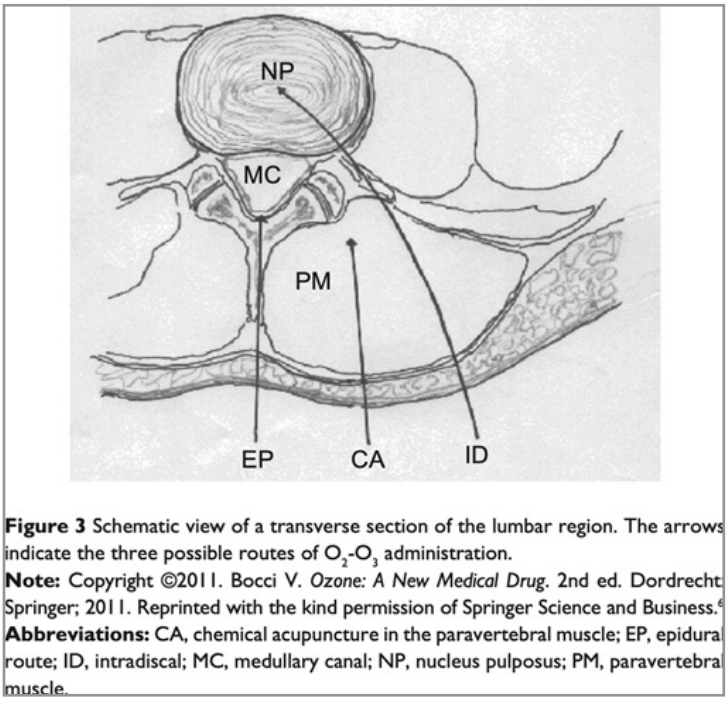

Figure 3 Schematic view of a transverse section of the lumbar region. The arrows indicate the three possible routes of O_2-O_3 administration.
Note: Copyright ©2011. Bocci V. *Ozone: A New Medical Drug*. 2nd ed. Dordrecht: Springer; 2011. Reprinted with the kind permission of Springer Science and Business.[6]
Abbreviations: CA, chemical acupuncture in the paravertebral muscle; EP, epidural route; ID, intradiscal; MC, medullary canal; NP, nucleus pulposus; PM, paravertebral muscle.

Figure 9: From: Drug Des Devel Ther. 2015 May 15; 9: Page 2679

Ozone concentration must be neither below 18–20 µg/mL, nor higher than 25 µg/mL. If it is too low, it is hardly effective, but higher than 20 µg/mL can be too painful, especially during the initial treatments, and may even cause lipothymia and a risk of vasovagal reflex. In a review of the literature Bocci observed that pain threshold usually rises after five to seven treatments and therefore the ozone concentration can be carefully increased, but not exceeding the limit of 30 µg/mL. The injection must be done very slowly using 35 mm needles varying from G22 to G25 according to the patient's obesity [9]. Most cases, two symmetrical injections (total dose 10–20 mL gas with at most 200–400 µg ozone) repeated twice per week for about 5–6 weeks (ten to 12 sessions) are sufficient; if not, the patient should be classified as unresponsive to this approach.

Paravertebral Approach through a Literature Review

Verga (1989) was the first to describe ozone intramuscular applications at the paravertebral level and trigger points in patients with chronic low back pain. Since the 90′s, oxygen-ozone injections have been administered into the paravertebral muscles, intervertebral discs, facet joints and neural foramina to achieve pain resolution. Needle tip positioning at target can be performed either with or without image-guidance based on fluoroscopy, computed tomography (CT) or rarely ultrasonography (US). In non-image guided procedures, the injection of O2-O3 mixture is targeted in the muscular paravertebral tissues localized at the level of pathologic intersomatic space. Conversely, image-guided procedures are based on peri radicular, intraforaminal or intradiscal injection of O2-O3 mixture at the level of the metamer of the herniated disc under image-guidance. These techniques (CT scan and Fluoroscopy with or without contrast) must be performed in an appropriate environment, imply exposure to ionizing radiation and frequently requires anesthesiologic support. There are no specific guideline or indication regarding the gold standard approach. In a recent review published at the end of 2021 in the European Journal of Radiology the authors conclusions were: "percutaneous oxygen-ozone injection is a minimally invasive, cost-effective, repeatable and highly available procedure for the treatment of lumbar disc herniation-related low back pain when poorly responsive to conservative treatments" [33]. Although there is no consensus to consider the superiority of image-guided injection vs non-image- guided, the first demonstrated a better therapeutic performance with higher impact on pain reduction and lower age-related variability [34, 35].

In acute lumbar disc herniation, conservative approach provides physical therapy and exercises or minimally invasive procedures as epidural steroid injection. However, patients may not respond to these treatments, sometimes treatments are not possible for side effects or contraindication to drugs or to the procedure. Physical Therapy (ultrasound, laser, TENS, thermotherapy…) are largely used in clinical practice, but their efficacy is not always supported by literature consensus. From this point of view paravertebral ozone injection (POI) is a relatively easy and less invasive technique that can be performed in outpatient clinic conditions without the need for sedation and radiological imaging. Well tolerated and therefore preferred as a complementary treatment by injection of oxygen-ozone directly into paravertebral muscles [36, 37]. In most studies conducted POI were administered to patient with chronic low back pain and to our best knowledge the study of Hamza and Nalan (Istanbul Gelisim University and Private Nisa Hospital, D.pt of Physical Medicine and Rehabilitation) published on Januar 2021in the Journal of Back and Musculoskeletal Rehabilitation; is the third one conducted in acute lumbar disc herniation (LDH) setting with a PC group. RCTs with a higher number of patients and longer follow-up periods are still needed. Further complications to limit conclusions about safety and efficacy were the lack of a standard treatment [38].

Another systematic review39 of 15 randomized controlled trials (20 years from2000 to 2021) exploring the role of oxygen-ozone therapy in LBP, reached similar conclusions. In fact, remarkable differences in ozone therapeutic protocols in terms of concentration and volumes, injection techniques, duration, and timing of the treatment; make study comparison very hard and shed shadows on the standardization of the procedure, which would be anyway essential to avoid potential drawbacks. Despite these flaws, some useful consideration can be drawn from the analysis of the literature. The results support the efficacy in reducing pain and improving functional status of LBP patients. In peri radicular and intraforaminal approach ozone probably normalize nerve function and its microenvironment. A sort of eutrophic effect plays by ozone that improves perineural microcirculation reducing local hypoxia due to both arterial compression and venous stasis [39]. Intramuscular Oxygen-Ozone Therapy (OOT) could also product a therapeutic effect on trigger points, in the paraspinal musculature [40]. On the other hand, a potential flaw could be related to the inaccuracy of the landmark- guided technique, especially in obese patients, lumbosacral junction abnormalities, such as sacralization of the L5 or lumbarization of S110 (Bertolotti Syndrome). New studies are exploring even more accurate methods of administration, particularly the use of ultrasound guidance [37]. Comparing the efficacy of paravertebral ozone with other treatments, Sconza find in all studies considered overall superiority over placebo, corticosteroids, and analgesic medications [39]. In 2020, Barbosa et al. performed a cross-sectional review using the PubMed, LILACS, and Scopus databases, which aimed at addressing the efficacy and adverse events occurrence of O2O3 in the treatment of LBP [41]. The authors concluded that the use of intramuscular– paravertebral O2O3 in LBP patients could be suggested as an effective and safe intervention, especially when compared to surgery.

In conclusion, intramuscular–paravertebral O2O3 therapy seems to be safe, rely- able and effective to reduce pain in patients affected by LBP not responding to anti- inflammatory/ analgesic drugs. Intramuscular–paravertebral O2O3 might be considered a promising technique that could be integrated as part of the multidisciplinary rehabilitation management of these patients [42].

Basic Principles of Oxygen Ozone Therapy

From a Retrieval of Literature Searching in MEDLINE © database from 1980 to July 2017. A work of Smith, Wilson and coll." Ozone therapy: an overview of pharmacodynamics, current research, and clinical utility" – Review Article [43].

Antioxidant Activity

Upon beginning O3 therapy, a multifaceted endogenous cascade is initiated and releases biologically active substrates in response to the transient, and moderate, oxidative stress that O3 induces. O3 can cause this mild oxidative stress because of its ability to dissolve in the aqueous component of plasma. By reacting with polyunsaturated fatty acids (PUFA) and water, O3 creates hydrogen peroxide (H2O2), a reactive oxygen species (ROS). Simultaneously, O3 forms a mixture of lipid ozonation products (LOP). Moderate oxidative stress caused by O3 increases activation of the transcriptional factor mediating nuclear factor-erythroid 2-related factor 2 (Nrf2). Nrf2's domain is responsible for activating the transcription of antioxidant response elements (ARE). Upon induction of ARE transcription, an assortment of antioxidant enzymes gains increased concentration levels in response to the transient oxidative stress of O3. The antioxidants created include, but are not limited to, superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione S-transferase (GST), catalase (CAT), heme oxygenase-1 (HO-1), NADPH- quinone-oxidoreductase (NQO-1), heat shock proteins (HSP), and phase II enzymes of drug metabolism. Many of these enzymes act as free radical scavengers clinically relevant to a wide variety of diseases.

O3, as well as other medical gases, e.g., carbon monoxide (CO) and nitric oxide (NO), has twofold effects depending on the amount given and the cell's redox status. There is a complex relationship between these three medicals gases. Hormesis is a potent, endogenous defense mechanism for lethal ischemic and oxidative insults to multiple organ systems. O3 may have a hormetic role in regulating the anti-inflammatory and proinflammatory effects of CO, including prostaglandin formation akin to NO, which has been shown to exert some of its biological actions through the modulation of prostaglandin endoperoxide synthase activity. Multiple studies have provided evidence that O3 therapy increased activation of the Nrf2 pathway via the induction of moderate oxidative stress. By doing so, a transient increase in H2O2 and LOPs enhances the number of antioxidants and therefore can be used for a longer time frame to reestablish the balance of the redox system. Systems have been proposed to have a more precise measurement of the redox state of a patient to achieve this goal. One system proposes simultaneously measuring different biological markers in the blood such as GSH, GPx, GST, SOD, CAT, conjugated dienes, total hydroperoxides, and TBARS. Using an algorithm, information can be gathered about the total antioxidant activity, total pro-oxidant activity, redox index, and grade of oxidative stress. Systems like this can provide insights to the correct dosage and response to O3 therapy based on oxidative stress levels seen in the patient.

Vascular Activity

O3 is a stimulator of the transmembrane flow of O2. The increase in O2 levels inside the cell secondary to O3 therapy makes the mitochondrial respiratory chain more efficient. In red blood cells, O3-AHT may increase the activity of phosphofructokinase, increasing the rate of glycolysis. By enhancing the glycolytic rate, there is an increase in ATP and 2,3-diphosphoglycerate (2,3-DPG) in the cell. Subsequently, due to the Bohr effect, there is a rightward shift in the oxyhemoglobin dissociation curve allowing for the oxygen bound hemoglobin to be unloaded more readily to ischemic tissues. Combined with the increase in NO synthase activity, there is a marked increase in perfusion to the area under stimulation by O3-AHT. With repeated treatment, sufficient LOP may be generated to reach the bone marrow acting as repeated stressors to simulate erythrogenesis and the upregulation of antioxidant enzyme upregulation. O3 also causes a reduction in nicotinamide adenine dinucleotide (NADH) and assists in the oxidation of cytochrome C.

O3 has also been shown to improve blood circulation and oxygen delivery to ischemic tissues.

Modulation of Immune System Response

In vivo, Ozone therapy has been shown to have multifaceted effects when interacting with PUFA. As stated previously, O3 reacts with PUFA and other antioxidants, H2O2 and varies peroxidation compounds are formed. H2O2 readily diffuses into immune cells has been shown to act as a regulatory step in signal transduction and facilitating a myriad of immune responses. Specifically, increases in interferon, tumor necrosis factor, and interleukin (IL)-2 are seen. The increases with IL-2 are known to initiate immune response mechanisms. Additionally, H2O2 activates nuclear factor-kappa B (NF-κB) and transforming growth factor beta (TGF-β), which increase immunoactivity cytokine release and upregulate tissue remodeling. H2O2 mediates the action of NF-κB by enhancing the activity of tyrosine kinases that will phosphorylate IκB, a subunit of the transcription factor NF-κB. Low doses of O3 have been shown to inhibit prostaglandin synthesis, release bradykinin, and increase secretions of macrophages and leukocytes.

Pathogen Inactivation Activity

When bacteria are exposed to O3 in vitro, the phospholipids, and lipoproteins that are within the bacterial cell envelope are oxidized. As this occurs, the stability of the bacterial cell envelope is attenuated. Moreover, evidence has demonstrated O3 to interact with fungal cell walls like bacteria. This disrupts the integrity of the cytosolic membrane and infiltrates the microorganisms to oxidize glycoproteins, glycolipids, and block enzymatic function. The combination of these reactions causes inhibition of fungi growth and mortality of bacteria and fungi.1,3,5 In vitro, O3 has been shown to interfere with virus-to-cell contact in lipid-enveloped viruses via oxidation of lipoproteins, proteins, and glycoproteins, thus interfering with the viral reproductive cycles [44, 45].

Anti-Inflammatory Activity in Musculoskeletal Disorders

The O2O3 might exert its action combining mechanical and anti-inflammatory effects, breaking glycosaminoglycan chains in the nucleus pulposus, decreasing their capability to retain water, thus lowering the size of the herniated position, and allowing to relieve the hernial conflict.

A reduction in disk volume is the result of all these events. Around the disc protrusion, inflammatory mediators prompted by granulation tissue are known to attract histiocytes, fibroblasts, and chondrocytes that can produce interleukin- 1α (IL-1α), interleukin-6 (Il-6), and TNF-α; these cytokines in-

duce the prostaglandin E2 pathway, which causes pain or increases the sensitivity of the nerve roots to other algogenic substances, such as bradykinin. In vivo, local injection of medical ozone would increase the concentrations of TNF-α, IL1β, and IFN-γ around the disc, suggesting that the contact of medical ozone with the disc damages the extracellular matrix, resulting in shrinkage and decompression of the surrounding neurons. This might proceed probably together with the decrease in lactic acid and inflammatory cytokines, resulting in the decrease of low back pain and sciatica. Furthermore, this disk shrinkage can enhance local microcirculation and increase oxygen supply by decreasing venous stasis caused by disk vessel compression. The O2O3 therapy might have analgesic and anti-inflammatory effects in treating disk herniation due to the neutralization of proinflammatory cytokines by boosting the surge of antagonists' release. When a disc degeneration leads to disc herniation, the adjacent nervous system structures, such as the nerve roots, or the dorsal root ganglion can be affected, causing neuropathic pain of mechanical or biochemical origin. Moreover, other spinal structures are damaged, including facet joints, ligaments, and muscles, which can also become pain generators [46].

Clinically, Niu et al. showed that low concentrations of medical ozone (20 and 40 μg/mL) can reduce the serum IL-6, IgG, and IgM expression, presenting as analgesic and anti- inflammatory effects; while high concentrations of medical ozone (60 μg/mL) increase the serum IL-6, IgG, and IgM expression, presenting as pain and pro-inflammatory effects. Thus, the medical ozone concentration of 40 μg/mL seemed to report the optimal treatment efficacy [47]. In conclusion, ozone therapy might reduce the autoimmune inflammatory reaction and, consequently, pain due to radiculopathy, after the exposure of the nucleus pulposus to the immune system.

Musculoskeletal disorders are considered as a common cause of pain and functional disability, predicting a burden that will further increase due to the aging of the population. They include all inflammatory and rheumatic diseases affecting the osteoarticular system such as osteoarthritis (OA). Discopathy often is associated with osteoarthritis of the vertebral bodies or of the posterior segment of the spine (Vertebral Facet Syndrome). Stiffness and functional limitation by sclerosis of the joints and calcification of the ligaments are often associated with myofascial disorders and usually with tender and trigger points.

Long-time exposure to chronic low-grade inflammation and imbalance in oxidant- antioxidant systems is involved in OA pathogenesis and progression by compromising the complex network of signaling pathways that regulate cartilage and subchondral bone homeostasis. A crucial role in this process might be played by inflammatory cytokines released by chondrocytes (IL-1β, IL-6, IL-8, IL-17, TNF-α, IFN-γ), promoting the catabolism of cartilage and subchondral bone. Under normal conditions, these catabolic factors are in equilibrium with anabolic factors that include anti-inflammatory cytokines (IL-4, IL-10) and anabolic cytokines (TGF-β, IGF-1, FGF-18, and PDGF) [48, 49]. O2O3 represents a promising treatment option for its ability to modulate inflammation, promote cartilage growth, and joint repair mechanisms. O3 might influence the modulation of inflammation through different mediators and signaling pathways [50].

Mechanical injury is the most important risk factor in osteoarthritis (OA) development. Although once considered a passive disease of mechanical attrition, injury drives active mechanosensitive intracellular signaling which affects the structural and symptomatic course of disease. Mechanosensitive signaling in cartilage has been elucidated over the years and two principal responses emerge: those that cause the release of growth factors from the matrix and which stimulate repair, and those that drive inflammatory signaling, a process that we have termed "mechanoflammation". The up-stream activator of "mechanoflammation" remains unknown, but it results in rapid activation of NFkB and the inflammatory mitogen activated protein (MAP) kinases and this controls the bioavailability of aggrecanase and regulation of nerve growth factor (NGF), causing pain. The precise relationship between mechanoflammation and cartilage repair is currently unclear, but it is likely that chronic "mechanoflammation" will contribute to disease by also suppressing intrinsic tissue repair [49].

Osteoarthritis (OA) is a primary cause of disability in the geriatric population, and common degenerative disorder affecting articular cartilage, synovium, and subchondral bone. Osteoarthritis (OA) is the most common joint disorder with a multi-factorial etiology including overproduction of ROS.

ROS overproduction in OA modifies intracellular signaling, chondrocyte life cycle, metabolism of cartilage matrix and contributes to synovial inflammation and dysfunction of the subchondral bone. In arthritic tissues, the NF-κB signaling pathway can be activated by pro-inflammatory cytokines, mechanical stress, and extracellular matrix degradation products. This activation results in regulation of expression of many cytokines, inflammatory mediators, transcription factors, and several matrix-degrading enzymes. Overall, NF-κB signaling affects cartilage matrix remodeling, chondrocyte apoptosis, synovial inflammation, and has indirect stimulatory effects on downstream regulators of terminal chondrocyte differentiation. Interaction between redox signaling and NF-κB transcription factors seems to play a distinctive role in OA pathogenesis [51].

Intramuscular O2O3 therapy is a safe and widely used procedure in the common clinical practice but these results could be only achieved starting from strict eligibility criteria in patient selection and trained and experienced physicians to perform the procedure.

Progression of OA involve alterations of reactive oxygen species (ROS) and NF- κB signaling pathways [51].

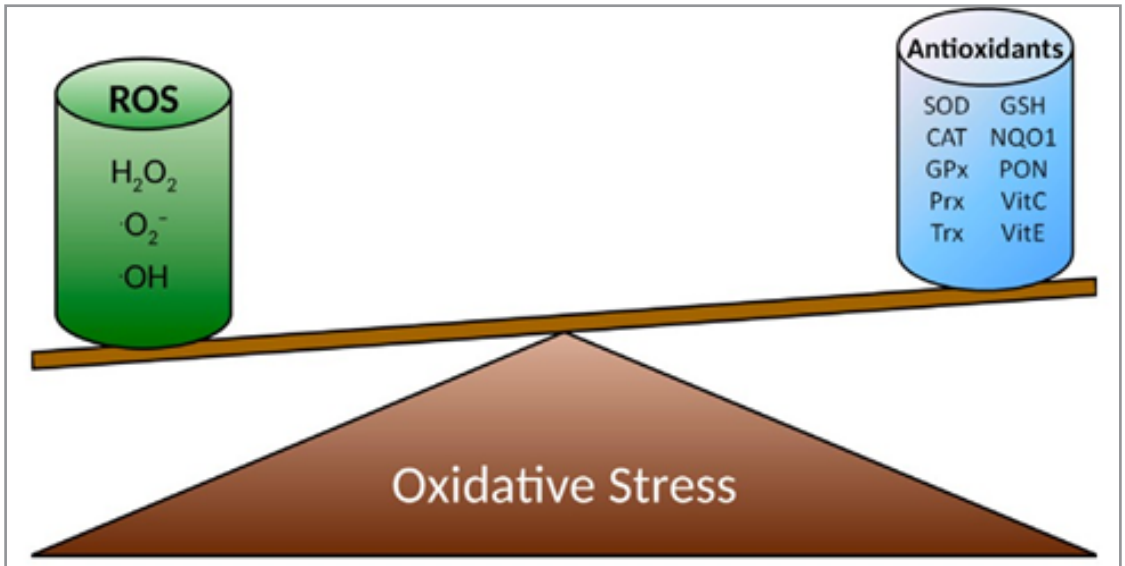

Fig. 1. Oxidative stress represents an imbalance between ROS and antioxidant enzymes. ($\cdot O_2^-$), superoxide anion; (H_2O_2), hydrogen peroxide; ($\cdot OH$), hydroxyl radical; CAT, catalase; GPx, glutathione peroxidise; GSH, glutathione; NQO1, NADPH ubiquinone oxidoreductase; PON, paraoxonases; Prx, peroxiredoxin; SOD, superoxide dismutase; Trx, thioredoxin; VitC, ascorbic acid (vitamin C); VitE, α-tocopherol (vitamin E).

Figure 10: From: Free Radical Biology and Medicine 132 (2019) Page 91

Additional Table 6: Orthopedic indications for O_3 therapy

Study	Pathology	Concentration and route of O_3 administration	Type of study	Measured parameter(s)	Results	Side effect(s)	Mechanism of action
Steppan et al.[64]; Paoloni et al.[65]; Oder et al.[66]; Magalhaes et al.[67]	Herniated lumbar discs	Intradiscal and extradiscal injection (1–3 mL O_2/O_3)	Meta-analysis (n = 12)	Meta-analysis for pain levels (visual analog scale)	Significant mean improvement of 3.9	Significantly low complication rate (0.064%)	Redox capabilities allow proteoglycans in the nucleus pulposus to be oxidized, leading to a small decrease in volume of the nucleus pulposus. Decreased volume decreases pressure and attenuates pain. O_3's anti-inflammatory effects due to the redox properties are also speculated to have analgesic effects. O_3's disinfectant properties are beneficial when using intra- and extradiscal injections because it lessens the risk of infection
				Meta-analysis for functionality (ODI)	Significant mean improvement of 25.7		
				Meta-analysis for functionality (modified MacNab)	Likelihood of showing improvement was 79.7%		
Al-Jaziri et al.[68]	Spine and joint osteoarthritis	Intra-articular and paravertebral muscle injections (20 μg/mL)	Prospective study (n = 220)	Pain level after 4, 8, and 12 sessions	Significantly decrease (P = 0.005, P = 0.005, P = 0.0043, respectively)	None	Ability to activate enzymes catalyzing peroxide reactions allowing for protection against ROS and peroxides. O_3's anti-inflammatory, analgesic effects, and anti-oxidative effects, taken together with the significantly decreased pain levels long-term, allows for speculation on possible histological changes after using O_3 therapy
				Follow-up pain levels (mean follow-up time is ~10 months)	Significantly decrease (P = 0.0048)		
Bonetti et al.[69]	First degree spondylolisthesis and spondylolysis	CT-guided bilateral periganglionic infiltration of O_2-O_3 and O_2-O_3 injection into lysis point of neural arch ¼ mL O_2-O_3 gas mixture at 25 μg/mL)	Prospective study (n = 18)	Pain levels after treatments using modified MacNab	15 patients (83.3%) had complete remission of pain. 3 patients (16.7%) had poor levels of improvement	None	By injection, the gas mixture directly proximal to the lysis points allows for analgesic and anti-inflammatory actions on the meningeal branches of a spinal nerve. Also, prostaglandin and cytokine levels are balanced because of O_3's ability to increase SOD production and to reduce ROS. Local improvement in circulation after treatment allows for increased eutrophic delivery
				Pain levels at 1-month follow-up using modified MacNab	15 patients (83.3%) had complete remission of pain. 3 patients (16.7%) had poor levels of improvement		
				Pain levels at 3-month follow up using modified MacNab	13 patients (72.2%) had complete remission of pain. 2 patients (11.1%) had satisfactory levels of improvement of pain. 3 (16.7%) patients had poor levels of improvement		
				Pain levels at 3-month follow up using modified MacNab	13 patients (72.2%) had complete remission of pain. 2 patients (11.1%) had satisfactory levels of improvement of pain. 3 patients (16.7%) had poor levels of improvement		

Note: O_3: Ozone; O_2: oxygen; ODI: Oswestry Disability Index; CT: computed tomography; ROS: reactive oxidative species; SOD: superoxide dismutase.

Figure 11: Orthopedic indications for O3 Therapy - From Med Gas Res. 2017;7 (3):212-219

Ozone Low Dose Concept

Ozone act as bioregulator. Using rheumatoid arthritis as prime example of chronic inflammatory disease, R. Viebahn and S.Léon Fernández demonstrate the bioregulatory role of ozone in an article published in the "International Journal of Molecular Sciences" in July 2021 [52]. Rheumatoid arthritis RA as a model for chronic inflammation: RA, in preclinical and clinical trials, reflects the pharmacology of ozone in a typical manner: SOD (superoxide dismutase), CAT (catalase) and finally GSH (reduced glutathione) increase, followed by a significant reduction of oxidative stress. Inflammatory cytokines are downregulated. Accordingly, the clinical status improves. The pharmacological background investigated in a remarkable number of cell experiments, preclinical and clinical trials is well documented and published in internationally peer reviewed journals.

The biochemistry of life is a kaleidoscope of dynamic processes, dynamically interacting equilibria in an almost confusing network. If individual cycles, partial balances, are disturbed, this biological network is still able to compensate for disturbances, repair defects, and keep the overall system "viable" for a long time.

Long-lasting disturbances, chronic stress, a multitude of different disturbance factors at various points of our biological network leave lesions within single or multiple dynamic, biochemical equilibria that can no longer be compensated and block the biological repair mechanisms. This mostly leads to chronic diseases.

Reactivating biological processes and, if possible, restarting the repair mechanisms is the target of Biological Medicine. In diseases with chronic oxidative stress, medical ozone has a special significance. At low concentrations and dosages, it acts as a bioregulator, while the regulation is blocked when high concentrations are used. In a biological system that can still be regulated, this role is incumbent on hydrogen peroxide H2O2, which is one of the most important oxidative bioregulators at biological concentrations. When and if the H2O2 concentration is too high, regulation is blocked and degenerative processes begin, as in the case of chronic inflammatory diseases.

From the work above mentioned two figures explain respectively the role of hydrogen peroxide as key redox regulator in the biological system (Fig. a) and the low dose ozone concentration as bioregulator (Fig. b) [52].

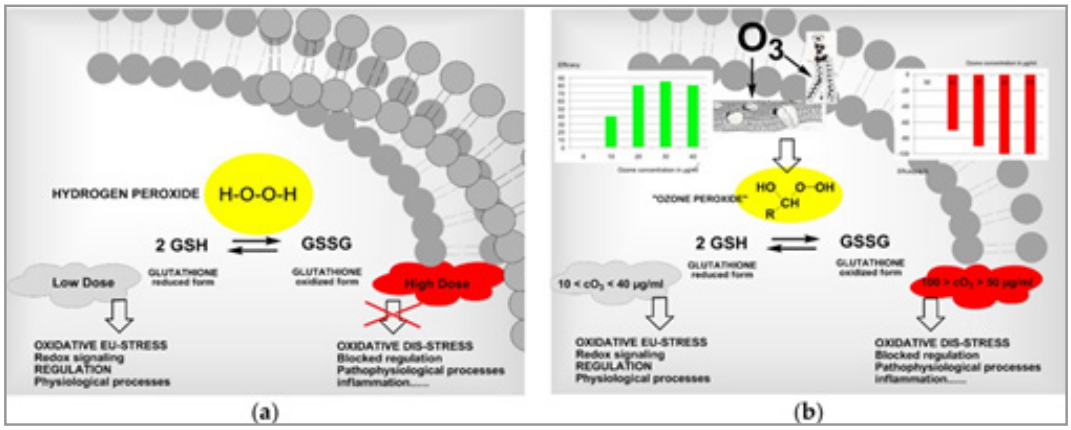

Figure 12: From: Int. J. Mol. Sci. 2021,22,7890

In its dose–response medical ozone follows the principle of hormesis: low concentrations (or doses) show a high efficacy, which decreases with increasing concentrations, finally reversing into an ineffective and even toxic effect. Figure 13 shows the efficacy/concentration relationship for the systemic application of ozone. Here, concentrations of 10–40 µg/mL represent those levels which are physiologically effective and recommended for systemic application.

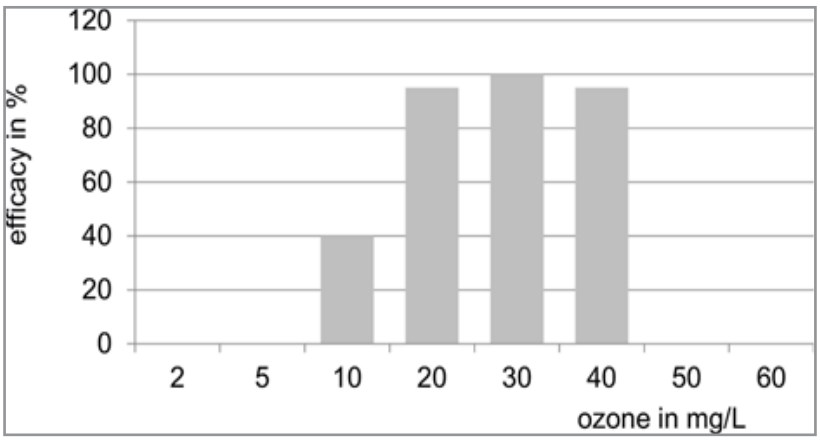

Figure 13: From R. Viebahn and Léon Fernandez Int. J. Mol. Sci. 2021,22,7890

Ozone-produced peroxides explain some pharmacological effects of ozone (Fig.14)

1. improved oxygen release by the red blood cells (RBC) through activation of RBC metabolism.
2. Immunomodulation through activation of the white blood cells (WBC) and signal transduction via nuclear factors.
3. Regulation of cellular antioxidants via Nrf2 signaling.

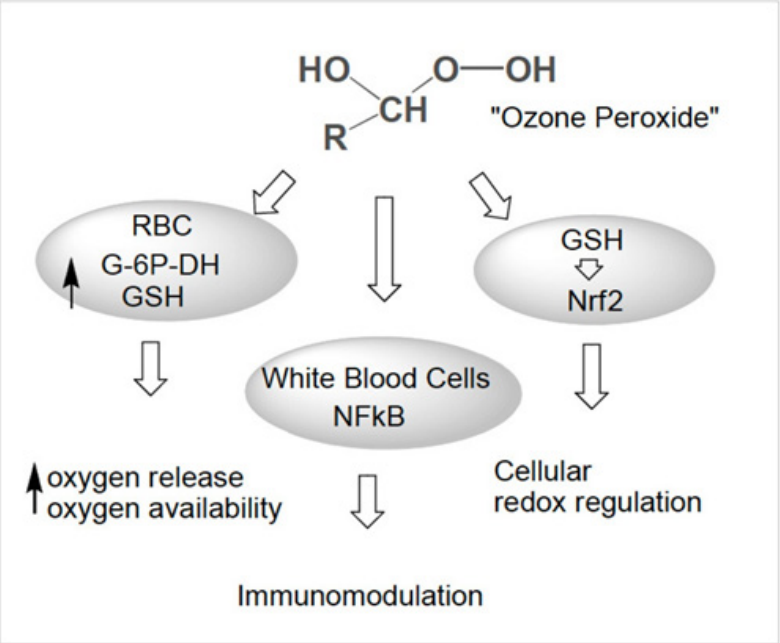

Figure 14: From: Viebahn and Fernandez Int. J. Mol. Sci. 2021,22,7890

Safety and Contraindications of Ozone Therapy

Considerations about safety and contraindication of Ozone Therapy are those published in a review article published on 23 February 2022 from a Spanish multidisciplinary group of Authors (Hidalgo-Tallón, Luis Miguel Torres-Morera, Jose Baeza-Noci and Others) [53].

All authors agree on the high safety of treatments with ozone therapy, especially by modern medical ozone generators with great precision.

Infiltrated ozone at concentrations between 4 and 30µg/ml is useful for treating musculoskeletal diseases such as arthritis, tendonitis, myositis, fasciitis, neuritis, or myofascial pain. Regarding dosage, standardized protocols are lacking [53].

Most authors relate the amount of the gas mixture to the extension of the injury or to the size of the joint cavity to be infiltrated. Generally, the amounts of gas range between 5 and 15ml, and ozone concentrations range from 4 to 30 µg/ml. The number of infiltration sessions usually ranges from 3 to 10 (usually one or two per week) depending on the specific evolution of each case. About intradiscal injection, 2ml for cervical and 5 for ml is the most used amount. If a patient does not respond to treatment after two or three interventions (once every 2 weeks) it is considered a failure. This lack of standardization in the treatment protocols makes difficult to compare results when performing a systematic review, not allowing to get high quality conclusions or recommendations. For knee osteoarthritis and lumbar disk herniation, evidence on safety and efficacy from systematic reviews and meta- analysis, according to the quality of the evidence proposed by the Scottish Intercollegiate Guidelines Network (SIGN), including GRADE criteria, are high (1+ and 2+ studies) and allow a recommendation level B, the same observed in most of the techniques used presently in pain units (SIGN, 2019) [54]. However, for the rest of potential indications, the evidence level is low, and ozone must be used only when other conventional treatments have failed or in a compassionate way.

Some recent publications remark that the ozone administration does not close the path to surgery in case of failure [9, 34].

It is worth mentioning that the efficacy of ozone therapy in the treatment of failed back surgery syndrome (highly prevalent among spine-operated patients, and usually worsens with new surgeries) represents a challenge. In these patients, we observe fibrosis due to epidural and perineural scars, paravertebral spasms, and neural adhesions, whose chronic inflammatory stimulus would lead to neuroplastic phenomena with central and peripheral sensitization. Theoretically, the fibrinolytic, anti- inflammatory and antioxidant properties of the infiltrated O2/ O3 would make it ideal for the treatment of these processes but more studies are needed. From the evidence found, ozone minimally interventional procedures are promising but we are far away to establish a recommendation. At least, prospective comparative studies should be done to whether recommend them or not [55].

Jacobs (1982) published that the incidence of effects adverse effects of systemic ozone therapy was only 0.0007%, mainly nausea, headache, and fatigue. In Cuba, with 25years of experience, having at least one ozone therapy unit per province of the country, only slight adverse effects have been recorded [53].

The experience of Italian experts is similar, although Dr. Bocci describes at least six deaths from gas applications in a direct intravenous way, a practice not recommended by scientific associations [56].

Eventually, the most serious common adverse effect would be a vagal reaction, generally associated with pain during infiltration. It is necessary to note that the injection must be done slowly, especially if a large gas volume at a high concentration is used [57]. However, some other complications have been reported in the literature, most of them due to malpractice or without a causal relationship between the ozone administration and the adverse event [58-62]. Most of them disappeared in a few days not needing specific medical treatment.

An absolute contraindication is severe glucose-6 deficiency phosphate dehydrogenase (favism), as this enzyme is necessary for supply hydrogen ions to the glutathione system, responsible for buffering the oxidation that lipoperoxides will produce in red blood cells [63].

As relative contraindications to systemic ozone therapy would be uncontrolled hyperthyroidism, thrombocytopenia, severe cardiovascular instability, and seizure states. It is also not advisable to use systemic ozone therapy in pregnant patients as it has not been deeply tested [53]. Infiltrations should be avoided following the general criteria described in the literature [64].

Undoubtedly, ozone therapy should be practiced by a well-trained doctor and, in patients with a poor general condition, a diagnosis of the pro-oxidant/antioxidant status of the patient would be advisable. One of the tools is the oxidation balance monitoring to give patients the maximum possible benefit in according to hormesis response that characterize ozone treatments.

Ultrasound: Role and Approaches in LBP

Possible Role of Ultrasound in Guided or Assisted Procedure

The clinical use of ultrasound has gained increased popularity in many operative setting and application procedures. In the last decades image quality has greatly improved and the machines have become portable, relatively inexpensive, and simple to use. Ultrasonography permits in the modern anesthesia practice to visualize the neural target, the surrounding structures, needle advancement and the spread of the injected mixture. Musculoskeletal ultrasound is a non-invasive, rapid, safe, emits no ionizing radiation, and can be performed in the outpatient clinical setting. Ultrasounds provide a real-time dynamic tissue assessment, allows exploration of the musculoskeletal system, therefore ideally suited for image- guided interventions. The basis of image-guided intervention is the ability to identify the region to be injected (target), confirm placement of the needle at the appropriate location thereby minimizing risks of injury to adjacent structures, and ensure correct localization of therapeutic agent. Recently, an increasing number of physicians have integrated musculoskeletal ultrasound into their clinical practices to ensure patient care [10]. With specifically regard to Oxygen Ozone therapy, in the daily practice, image-guided procedures are based on periradicular, intraforaminal or intradiscal injection of O2-O3 mixture at the level of the metamer of the herniated disc under image-guidance. In non-image guided procedures, the injection of O2-O3 mixture usually is targeted in the muscular paravertebral tissues localized at the level of pathologic intersomatic space. In one metanalysis published at the end of 2021 on the European Journal of Radiology imaging-guided procedures showed better performances compared to non-image-guided techniques based only on anatomical landmarks, with higher therapeutic efficacy and lower age-related variability in clinical results [33]. An original paper published in February 2021 by Sconza, Braghetto, and others on International Orthopaedics describe the clinical outcomes following US-guided periradicular injection of oxygen-ozone as a treatment option for low back pain associated to sciatica in patients affected by symptomatic L5-S1 disc herniation [40]. Despite the little dimension of statistical sample, the conclusion was that ultrasound can improve both low back and radiating pain. The authors evaluated the improvement in functional scales and the reduction of kinesiophobia, but results were modest considering the perception of patients' quality of life evaluated by SF-12. Authors postulated these finding with the inclusion in the study of patients with chronic LBP, in whom the quality-of-life improvement is not only related to pain reduction but also to complex physical and psychological aspects. Latini in a review explains the numerous promising ways in which ultrasonography can be useful in oxygen-ozone practices for musculoskeletal disorders [10]. If injected into the paravertebral muscles, ozone is rapidly dissolved in the interstitial water and quickly reacts with antioxidants, affecting just an area up to 3 cm from the injection site depending on the dose. Therefore, the opportunity of applying ozone closer to the disc and, particularly, the possibility to precisely target the nerve root was hypothesized to be a more effective treatment especially for radicular pain, maintaining anyway its therapeutic effects on paravertebral and periradicular soft tissues.

Morselli (author cited from Latini10) speculated that the better accuracy provided by USG injections could allow the use of a smaller volume of O2-O365. This could be a relevant aspect since the use of a large volume of ozone in a single administration may create discomfort to the patient or cause possible side effects, such as acute muscular or deep visceral pain, burning, and heaviness sensation until vagal crisis. In that study, the use of 5ml ozone injections resulted in the same results in terms of VAS decrease compared to 10 ml administration, but without discomfort for the patient. This is an interesting observation that deserves further study, especially in the long-term evaluation and using a more rigorous methodology.

Using an ultrasound probe, it is possible to target the needle and evaluate the gas distribution in the tissues near the nerve root and the facet joint. Paravertebral injections might be a direct effect on trigger points in the paraspinal musculature. Both needle and gas injection have a similar role to dry needling of trigger points, as demonstrated in patients with myofascial pain syndrome or low spinal pain. This phenomenon has been regarded as "chemical acupuncture".

In 2015 Morselli hypothesized that, in order to maximize the benefit of ozone, the injections should be as close as possible to the articular facet, concluding that US allows the physician to integrate the landmark-guided approach with the aim of improving the procedure accuracy and safety [65]. Today we can say that ultrasound guidance allows the physician to apply ozone closer to the disc, precisely target the nerve root, and evaluate the nee-

dle path and gas distribution, improving the accuracy and safety of the procedure. The use of combined treatment with paravertebral and periradicular OOT injections could also be proposed to obtain both therapeutic effects on the paraspinal musculature and on the nerve root [40].

Ultrasonography, used as a pre-procedure assessment before the paravertebral infiltration, is useful to identify the needle length range most suitable to perform infiltration. Ultrasonography allows more precision following in real time every step of the procedure. Post-procedure valuation, ultrasonography allows confirming the optimal distribution of the O2–O3 mixture injected in the tissue, therefore may be an added value to improve procedural accuracy, maximize patient's safety, and optimize clinical outcomes [10].

A specifical limit of ultrasonography is the different acoustic impedance between soft tissues and the bone cortex that allows only the evaluation of the bone surfaces. It is well known the phenomenon of **acoustic shadowing** (also called **posterior acoustic shadowing**) characterized by a signal void behind structures that strongly absorb or reflect ultrasonic waves. It is a form of imaging artifact. Since sound waves cannot penetrate bones, this imaging ultrasound-technique is not reliable for intervertebral discs procedures. The high-frequency sound waves used in ultrasound cannot penetrate the tissue to any significant depth; therefore, deep structure imaging is not possible by this technique. In contrast, low-frequency sound waves can enter deeper into the tissue but generate images at lower resolution. In degenerative disc or prolapsed disc disease interventional procedures are usually performed with fluoroscopy, CT scan or MRI. Searching literature to our best knowledge we found no evidence of ultrasound as reliable paravertebral approach for foraminal or discs procedures at lumbar spine level, mainly for the physical reasons mentioned above.

One of the chief limitations for ultrasound guidance in lumbar spinal procedures is reduced visibility in patients with obesity.

Despite these limits, ultrasound confirm his value as diagnostical assessment for subcutaneous tissue, muscular plans, fasciae, ligaments, and tendons. It is worth mentioning that are increasing evidence in ultrasound to evaluate the thickness of the transversus abdominis (TrA) muscle or multifidus muscles. All this would be important in rehabilitation field to start specifically functional rehabilitative program or simply to measure the results of exercises program. By assessing the muscle performance, ultrasound play an important role to evaluate core stability and others postural aspects. Beyond the topic of this literature review but important especially in non-specifically low back pain.

A recent review of anesthesiologic interest and concerning neuraxial blocks, summarized that ultrasound preprocedural imaging helps to identify the midline, vertebral level, interlaminar space, and can predict the depth to the epidural and intrathecal spaces. By providing information about the best angle and direction of approach, in addition to the depth, ultrasound imaging allows planning an ideal trajectory for a successful block reducing complications [66].

Proposed benefits of US include lower cost and avoidance of radiation exposure for patients and medical personnel. Although there is great interest in expanding the use of US, there are new challenges with its application to lumbar facet–targeted procedures including increased tissue depth in the lumbar region. The technological limitations of US combined with the tissue depth of lumbar facets may affect the accuracy of needle placement. As reported in a recent meta-analysis published from Ashmore and others in 2022 is critically important when facet-targeted procedures are used for diagnostic purposes [67]. All studies which specified the target for needle placement in medial branch block (MBB) described the junction of the cephalad transverse process and the superior articular process which has been shown in a cadaveric and CT-confirmation study as being less specific than targeting a lower point midway between the upper border of the transverse process and the mamillo accessory ligament. Similar considerations can be made for facet joint injections (FJI). Ultrasound technology is based on the piezoelectric principle, whereby electrical current passing through crystals in the US transducer are converted into pulsed sound waves. These ultrasonic waves are transmitted into the targeted tissues and reflected back to the transducer. High frequency transducers with shorter pulse length yield a higher resolution image. However, resolution is substantially limited when visualizing deeper structures because of attenuation of sound waves through the intervening tissues. Depth gain compensation can correct for the loss of acoustic energy through attenuation but for deeper structures, depth gain compensation is inadequate for optimal visualization. Individual patient factors such as increased BMI and variations in adipose tissue distribution can contribute to suboptimal resolution. Thus, it can be posited that the technological limitations of US and individual patient factors are key contributors to the lower accuracy of US-guided MBB and FJI. The use of US may also be considered when diagnostic accuracy is a secondary concern. For example, as suggested by the findings of the meta-analysis of Wu et al., the therapeutic effects of US-guided FJI may not be affected by inaccurate needle placement; thus, US may be an acceptable imaging modality for these injections [68]. As wrote Cohen in a Consensus practice guidelines on interventions for lumbar facet joint pain from a multispecialty, international working group (Regional Anesthesia Pain Medicine - 2020) ..." There are few conditions in interventional pain medicine as controversial as lumbar facet joint pain [69]. Everything from incidence to diagnostic criteria, patient selection for interventions and the effectiveness of treatment is a source of contention and scientific debate. Regarding prevalence, the cited frequency of lumbar facet joint pain ranges from as low as 4.8% to over 50%. The wide disparity in reported prevalence raises questions regarding the accuracy of diagnostic testing in the absence of any non-interventional diagnostic reference standard. The poor correlation between facet joint pathology on imaging and LBP further fuels debate".

Starting from considerations and results of the studies cited above, we take in account two ultrasound approach to target the facet joint periarticular space [65, 68-70]. We could postulate that zygapophyseal-joint plane is deeper than paravertebral muscles and closest to periforaminal space.

In consideration of the fact that we use a "gaseous medium" we could count on a greater diffusion towards structures otherwise unreachable. Therefore, effects close to a periradicular or paraforaminal injection with lower risk and a shorter learning curve.

Indeed, each facet joint receives dual innervation from the medial branch of the dorsal ramus of the nerve arising at the same level and also the medial branch of the nerve one level above. In the facet joints there are also mechanoreceptors lining the facet capsule, so they may also have proprioceptive functions. Nociceptive and autonomic nerve fibers have been identified in the capsule of the facet joints, subchondral bone and synovium. From point of view of Precision Medicine, in non-acute LBP often characterized by multiple pain generators, probably a more effective strategy.

Pre-Procedure Assessment Before Paravertebral Infiltration

Intramuscular paravertebral injection10 of O2–O3 mixture is a technique used frequently in clinical practice to treat spinal diseases and administered in the paravertebral muscles corresponding to the metamer of each vertebral segment affected. Symmetrical injections of 5–10 mL of O2–O3 gaseous mixture (15–20 µg/mL concentration) for site were performed, via an extraspinal lateral approach. Needles for lumbar regions from G22 to G25 and length changes according to the patient body size. Under sterile conditions, medical O2–O3 mixture is injected at 2 cm laterally from spinous processes in the paravertebral muscles, making sure not to be inside a blood vessel. The gaseous mixture should be introduced very slowly in order to avoid pain and promote homogeneous distribution of the gas through the muscle fibers. Individuation of surface anatomical landmarks is fundamental. In lumbar region, the L3–L4 intervertebral level can be estimated from an imaginary horizontal line across the top of the iliac crest (Tuffier Line). The spinous process of L4 is identified by palpating as a large and sagittal ridged eminence, while the spinous process of L5 is described as a deep, small bony point, identified caudally from L4. Ultrasonography can be used to integrate the landmark-guided approach to improve accuracy and safety of the treatment. Ultrasonography allows a detailed pre-procedural examination of the area of interest, identifying and characterizing the various anatomical structures at the lumbar level. In the paramedian oblique sagittal scan, the probe is placed approximately 2 cm lateral to the midline in the sagittal axis and it is tilted softly medially toward the midline (paramedian sagittal oblique view). In this view, the sacrum is identified as a flat hyperechoic structure with a large acoustic shadow anteriorly. Procedure accuracy improves by the identification of the right intervertebral space. Sliding the transducer in a cranial direction, the gap between the line of the sacrum and the lamina of the L5 vertebra (with typical sonographic "sawtooth" appearance) represents the L5-S1 interlaminar space. (Fig. 15)

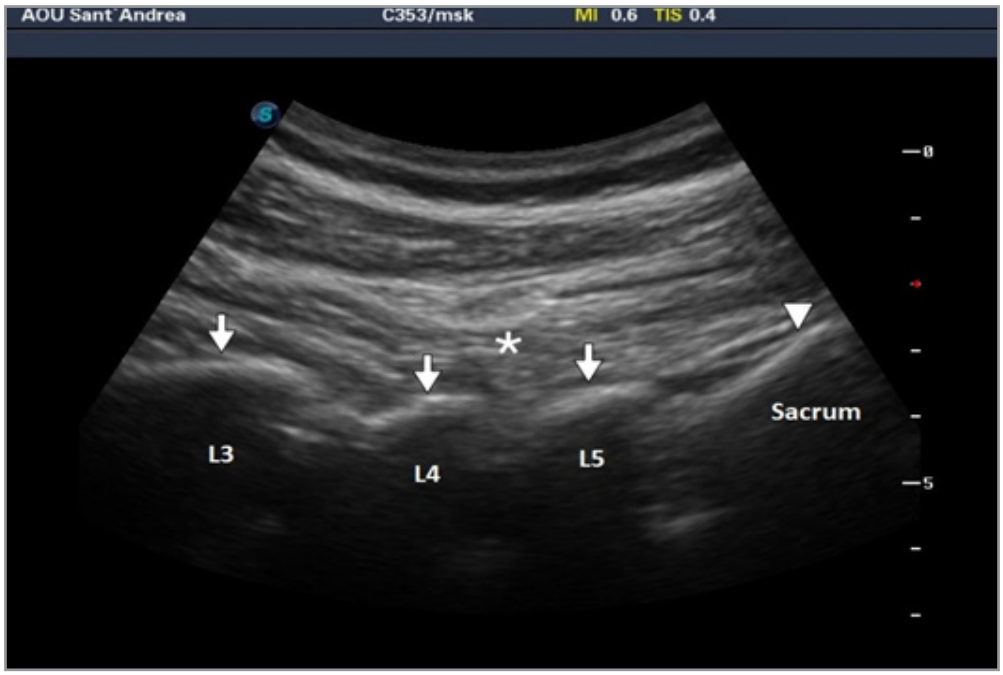

Figure 15: Paramedian Sagittal Obl. View. From Latini Med Gas Res 2019 Jan-Mar; 9 (1): Page 19

By placing each interlaminar space in the centre of the ultrasound screen, its position can be marked on the skin at the midpoint of the long axis of the probe. This prevents misidentification of the level during later scanning in the transverse plane. Two measurements provide useful information about paravertebral muscle depth and most suitable needle length range to perform infiltration:

- Skin-Muscle Distance (estimate minimum depth necessary to achieve the musculature and it is influenced by the thickness of the subcutaneous tissue).
- The Skin-Lamina Distance allows an assessment of the maximum paravertebral muscles' depth.

Precision to the target, low volumes, low concentration, and slow injection, decrease patient discomfort.

Post-Procedure Valuation of the Oxygen-Ozone Distribution

Once injected in the site to treat, ultrasonography may be useful tool to evaluate the O2–O3 mixture distribution in the tissue. O2–O3 mixture spreads in the tissue following the path of least resistance and is visible for a variable time. In intramuscular paravertebral injection, ultrasonography shows a homogeneous gas distribution through the paravertebral muscle fibers.

Lumbar Facet Joint Sonoanatomy

An accurate ultrasound evaluation of the lumbar facet joints can be performed in combination with the anatomical information obtained by sagittal and transverse scans. The ultrasound probe is placed over the lower lumbar spine approximately 3–4 cm lateral to the midline, in a parasagittal orientation (paramedian sagittal transverse process view). The transverse processes appear as hyperechoic curvilinear structures with finger-like acoustic shadowing beneath, separated by the hypoechoic striated psoas muscle. This sonographic pattern has known as the "trident sign" (Fig. 16-17).

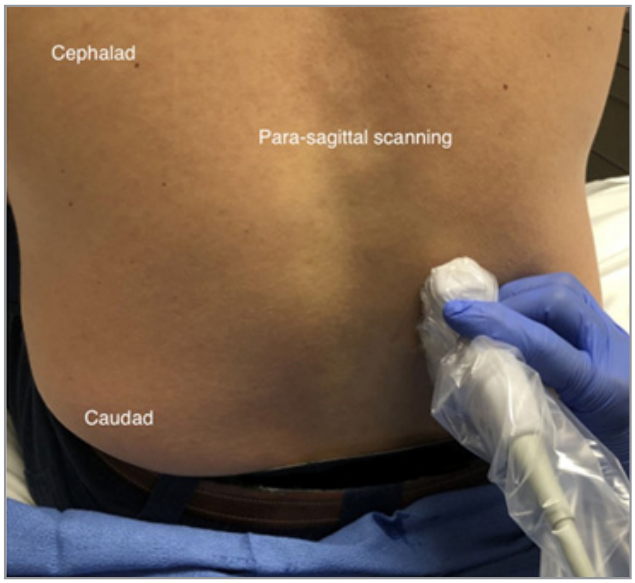

Figure 16: Para-sagittal Transv. Process view Scanning. From: Curr. Anesthesiol Rep (2021)11 Page 329

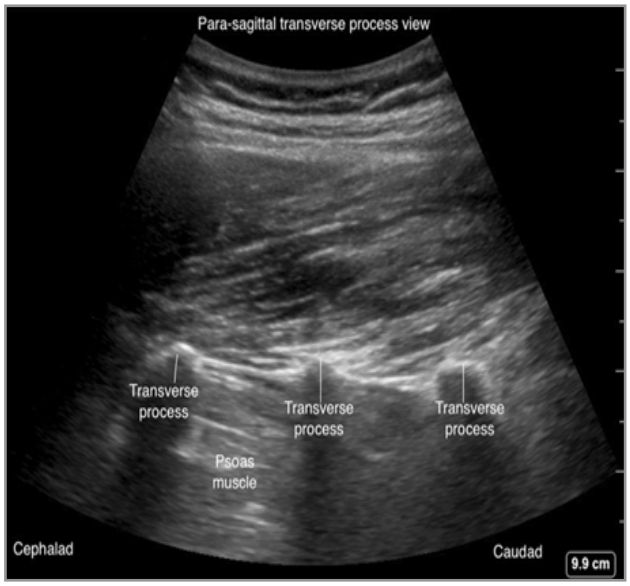

Figure 17: Para-sagittal transv. view (Trident Sign) - From: Curr Anestesiol Rep (2021) 11: Page 329

Maintaining a sagittal orientation, the transducer is moved medially until to observe the facet joints column, which appears as a continuous hyperechoic wavy line with acoustic shadowing beneath (paramedian sagittal articular process view).

In this view, the typical sonographic appearance resembles a series of camel humps ("camel-hump sign"), where each hump represents the facet joint formed by superior and inferior articular processes of the consecutive vertebrae (Fig. 18).

An accurate identification of different spinal levels can be determined by counting the facet joints from the lumbosacral facet joint toward cranial direction up or by a "counting-down approach" from the lower thoracic vertebrae or the upper lumbar spine, using the 12th rib as a landmark. The probe can be tilted softly toward the midline, performing a paramedian oblique sagittal scan, to improve the accuracy of ultrasound to identify spinal segments. A succession of "sawtooth" hyperechogenic lines visualized in this view, corresponding to vertebral laminae, allows identifying the intervertebral spaces from L5/S1 to L1/L2 (Fig.19). The facet joints lie in approximately the same transverse plane as the interlaminar space. An asymmetry of articular processes is suspect for a scoliosis of the column.

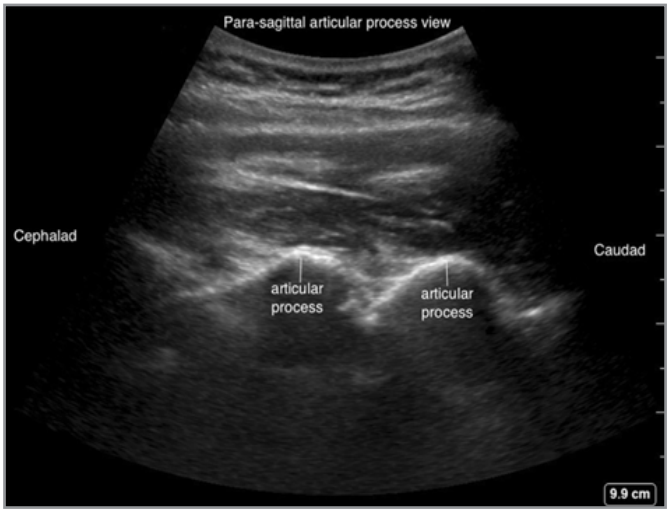

Figure 18: "Camel Hump" in Para-Sagittal View. From: Curr Anesthesiol Rep (2021) 11: Page 330

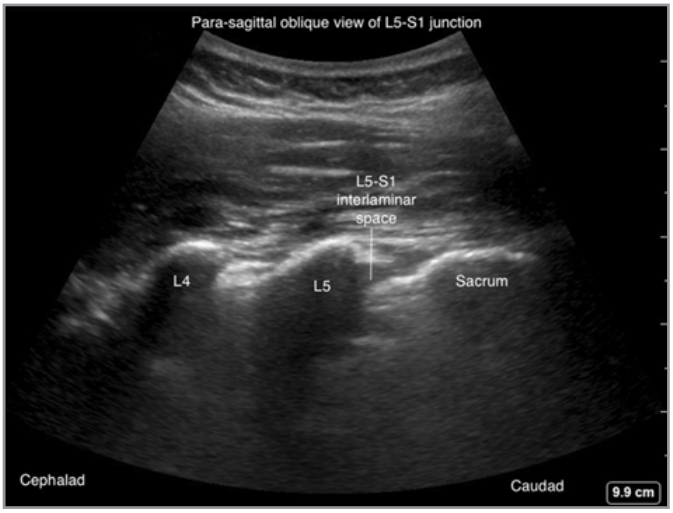

Figure 19: Para-sagittal oblique (interlaminar space) From: Curr Anesthesiol Rep (2021) 11Page 330

Processes in paramedian sagittal view are visible as a continuous hyperechoic line of "humps" with acoustic shadowing beneath and the bony contour of the superior articular process (SAP) is usually more superficial than the inferior articular process (IAP). The facet joint space is between articular lines of SAP and IAP. Erector Spinae Muscle (ESM) lies superficially to the articular processes (Fig. 20)

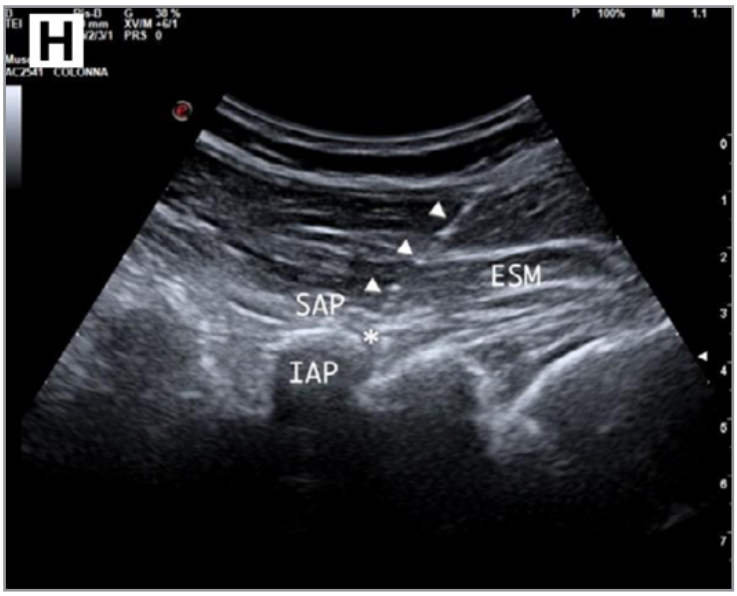

Figure 20: Paramedian Sagittal View - From. Med Gas Res. 2021 Ott. -Dic.;11(4): Page 148 Fig. 1H

An approach lateral to medial require a transverse interlaminar view. Interspinous ligament (ISL) is visible in the midline (hypoechoic midline vertical stripe). In a transverse scan the plane of zygapophyseal joint lies at the level of interspinous space. Spinous process is visible as a superficial hyperechoic line with vertical linear acoustic shadowing beneath, while at either side of the base of the spinous process the laminae appear as bright white horizontal landmarks. Lateral the spinous process and upon the laminae the erector spinae muscle can be visualized. (Fig. 21,22)

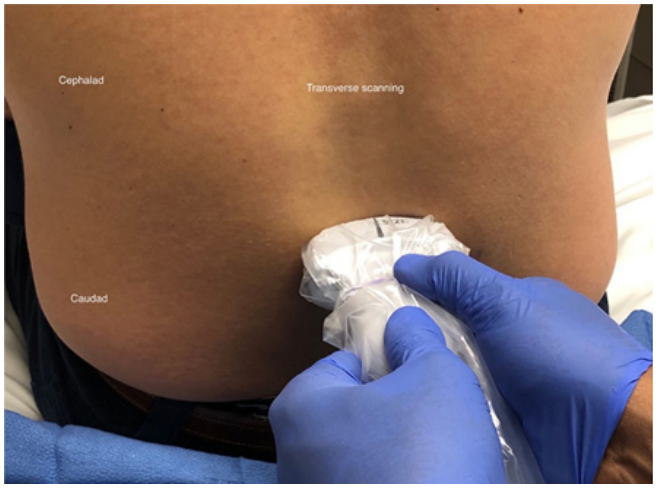

Figure 21: Transverse Scanning From: Curr. Anesthesiol Rep (2021) 11:Page 332

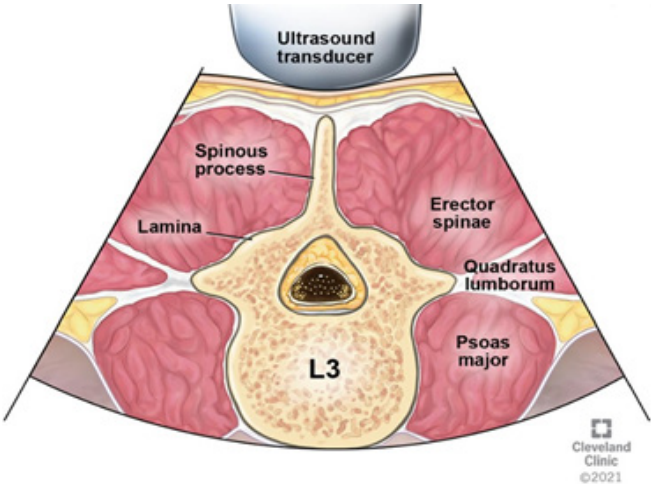

Figure 22: Transverse Scanning From: Curr Anesthesiol Rep (2021)11:Page 331

In transverse view IAP appear medially and SAP laterally. Interspace, the place where perform the facet joint injection (FJI). (Fig. 23-24)

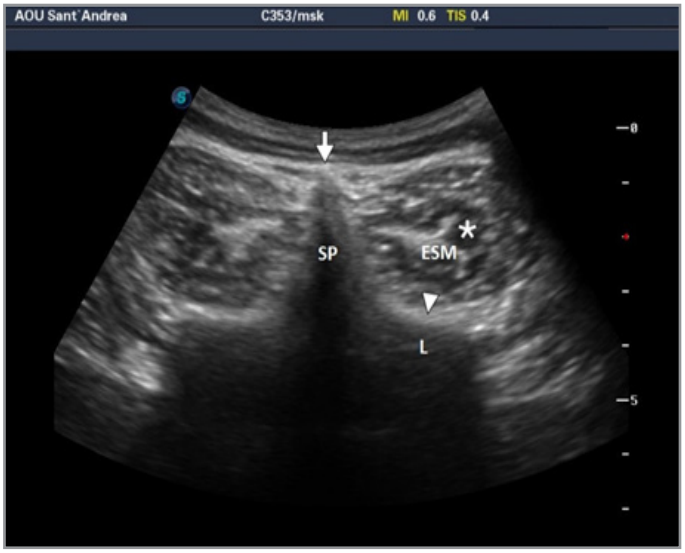

Figure 23: Transv. View of Spinous Process From:Latini Med Gas Res 2019 Jan-Mar;9(1) : Page 20

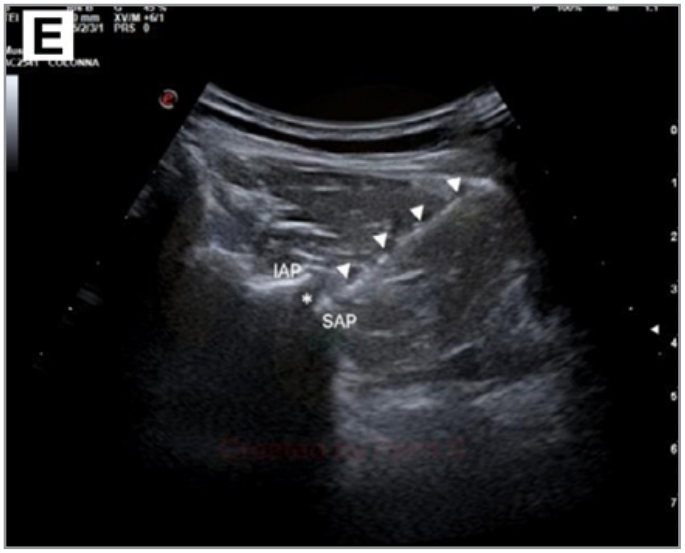

Figure 24: FJI and Interspace From: Latini Med Gas Res 2021; 11(4): Page 148

Zygapophyseal Periarticular Joint: Lateral to Medial Approach [70]

Patient placed in a prone position with a pillow under the abdomen to compensate for the lumbar lordosis. A convex probe with low frequency (3-8 MHz) is required for a better penetration and wild field of view to visualize spine anatomical structures located deeper. Improve recognition of anatomy reducing beam frequency, adjusting the depth, focus and TGC (Total Gain Compensation) or others gain settings. Anatomical information should be obtained by sagittal and transverse scans. Accurate identification of spinal levels by counting-down (using 12th rib as landmark) or by counting - up (from the Stealth Sign in transvers view over S1, or in longitudinal axis between sacral crest and 5th spinous process of L5). Once the appropriate lumbar spine level is visualized in the parasagittal views the probe is rotated to obtain a transverse sonogram of the facet joint. The target point is the middle portion of the joint, visible as hypoechoic space in the transverse sonogram. Under real-time sonographic guidance, a spinal needle (22 Gauge, 90 mm) is inserted 3–4 cm laterally from the midline on the lateral end of the transducer in- plane technique. The insertion angle is approximately 45° to the axial plane, and the needle advances in a lateral to medial trajectory. The needle is directed down to the junction between the medial aspect of the inferior articular process and the lateral aspect of the superior articular process. The in-plane approach allows visualizing throughout the entire procedure the complete needle path, which appears as a bright line in the transverse view.

Zygapophyseal Periarticular Joint: Caudal to Cranial Approach70

Performed in the paramedian sagittal process articular views. The articular processes are visible as a continuous hyperechoic line of "humps" with acoustic shadowing beneath, and the bony contour of the superior articular process is usually more superficial than the inferior articular process. The target point is the space between the articular lines of the superior articular process and inferior articular process. Under real-time sonographic guidance, a spinal needle (22 Gauge, 90 mm) is introduced on the inferior end of the probe in-plane technique. The insertion angle is slightly lower 45° respect to the longitudinal plane, and the needle advances in a caudal to cranial direction. The caudal to cranial approach allows performing the facet joint injection at various levels at the same time, with a single-needle insertion. Moreover, L5–S1 facet joint injection, harder to perform in lateral to medial technique owing to the proximity of the iliac crest, can be easily performed without obstacle the needle advancement.

Gross Anatomy and Sonoanatomy of the Lumbar Spine

Each vertebra is made up of a body and arch. The arch is composed of pedicles, a spinous process (SP), lamina, superior and inferior articular processes (APs), and transverse processes (TPs). The vertebral canal is formed by the spinous process and lamina posteriorly, pedicles laterally, and vertebral bodies an- teriorly. Within the vertebral canal lie the thecal sac and its contents. The epidural space lies outside the thecal sac within the vertebral canal. The identification of these key anatomical structures in para-sagittal and transverse views enables better performance of ultrasound-guided or assisted procedures.

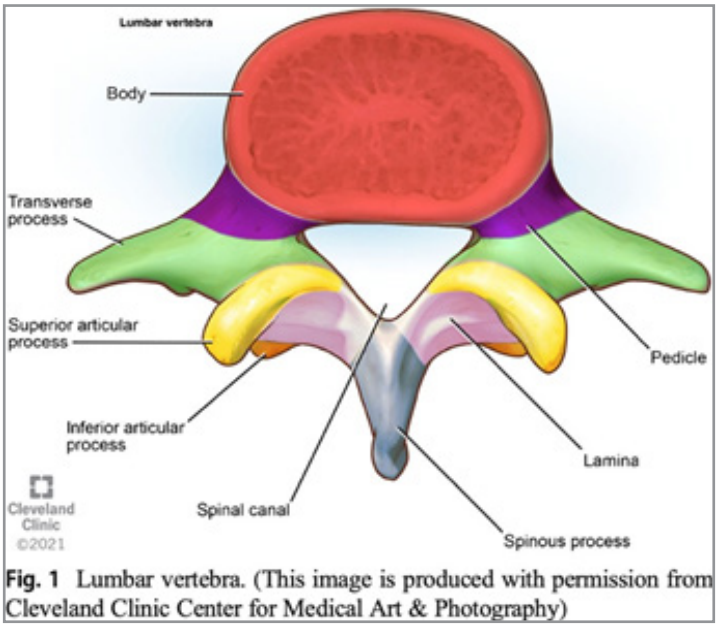

Fig. 1 Lumbar vertebra. (This image is produced with permission from Cleveland Clinic Center for Medical Art & Photography)

Figure 25: From Curr Anesthesiol Rep (2021) 11: Page327

The bony structures of the lumbar vertebrae appear as hyperechoic white lines on ultrasound imaging with black acoustic shadowing underneath. Figure 26 shows the interlaminar and interspinous spaces. The interlaminar space is located posterolateral and the interspinous space in the midline. Figure 27 shows intervertebral foramina that are located laterally. From foramina emerge the spinal nerve roots. The ligamentum flavum, epidural space, and posterior dura often appear as single or sometimes double hyperechoic white structure referred to as the posterior complex (PC). The anterior dura, posterior longitudinal ligament, and the posterior aspect of the vertebral body are visible as a single hyperechoic white line referred to as the anterior complex (AC). The anterior and posterior complexes can be visualized in both interlaminar and interspinous views. Between AC and PC lies the Dural sac.

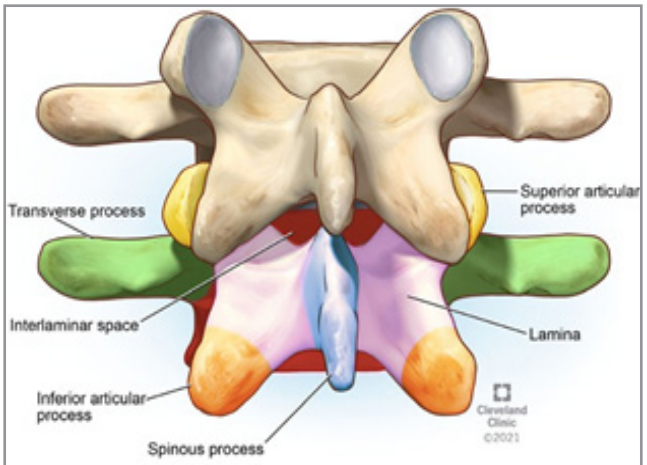

Fig. 2 Posterior view of adjacent lumbar vertebrae. (This image is produced with permission from Cleveland Clinic Center for Medical Art & Photography)

Figure 26: Interlaminar and Interspinous Space. From: Curr Anesthesiol Rep (2021) 11: Page 327

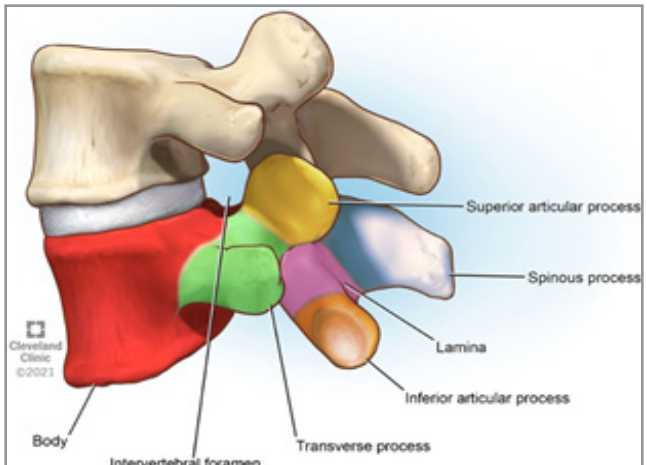

Fig. 3 Lateral view of adjacent lumbar vertebrae. (This image is produced with permission from Cleveland Clinic Center for Medical Art & Photography)

Figure 27: Intervertebral Foramina. From: Curr Anesthesiol Rep (2021); 11: Page 327

Ultrasound-Scan is performed in sagittal and transverse view for the correct location of intervertebral level, midline, and to achieve measures of the depth to the epidural space, facet joint plan or space, and identification other relevant structures. Conventionally, three para-sagittal and two transverse views are performed for complete neuraxial scanning [71].

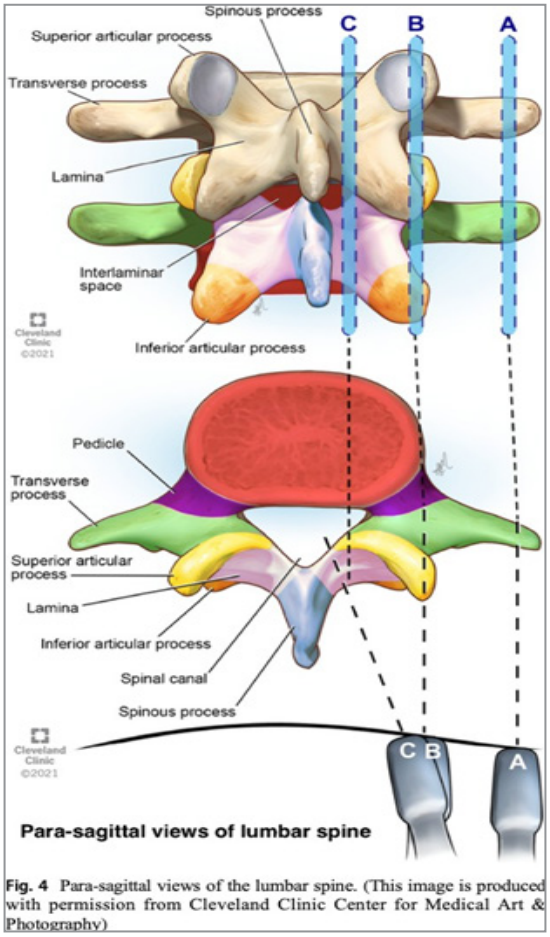

Figure 28: Para-Sagittal Views. From: Curr Anesthesiol Rep (2021); 11: Page 328

The ultrasound transducer is placed in a para-sagittal plane a few centimeters lateral of midline as shown in Fig. 28 (A). The surface of the transverse processes is seen as round hyperechoic outlines with deeper hypoechoic shadows as dark finger-like projections ("trident sign"). The psoas major muscle is seen between these hypoechoic shadows. (B) The probe is then moved medially (para-sagittal articular process view) until a continuous white hyperechoic line with "camel humps" is seen, indicating the facet joint's articular processes. It is difficult to see any neuraxial structures in this view as the bone is continuous and does not permit ultrasound signals beyond the articular processes. (C) From the para-sagittal articular process view, the probe is tilted medially toward the median sagittal plane to bring the lamina into view. This is the para-sagittal oblique view. The sloping lamina appears as white hyperechoic lines described as a "saw-tooth" or "horsehead" pattern. The gaps represent the interlaminar spaces through which the posterior and anterior complexes are visualized. This is the most important window in sagittal scanning to identify interspaces for a spinal or epidural injection.

Positioning the probe orthogonal to the spinous process line (rotated of 90° respect the sagittal scan) is possible to achieve a transverse spinous process view as shown in Fig. 29.

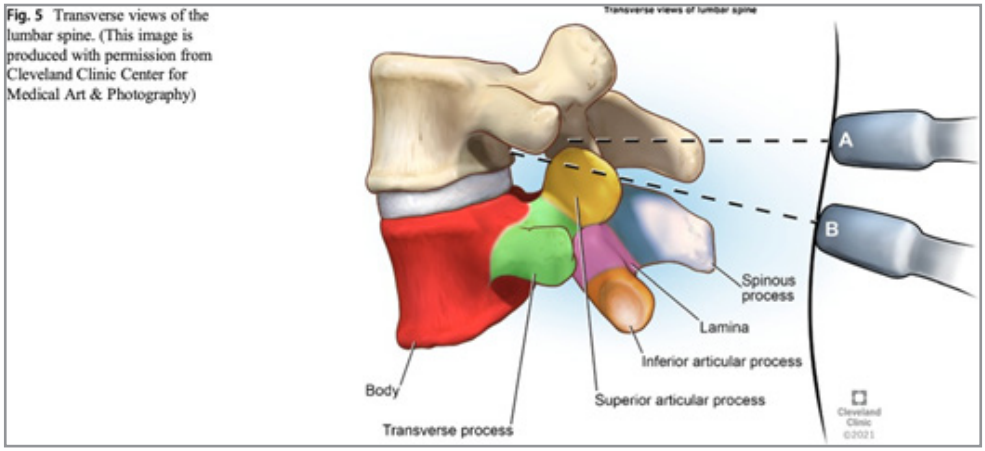

Figure 29: Transv. Spinous & Interspin. View. From: Curr Anesthesiol Rep (2021); 11: Page 329

The tip of the spinous process is identified as a white hyperechoic line with acoustic shadowing beneath it with a sloping lamina seen laterally. This is the key view for the identification of midline and the interspinous spaces between the consecutive spinous processes in obese patients. After identification of the spinous process, the probe is either moved cephalad or caudad to the interspinous space. This view, also known as the transverse interlaminar view, allows for visualization of the posterior and anterior complexes along with articular and transverse processes laterally. The intrathecal space is seen as hypoechoic space between the posterior and anterior complexes.

Discussion

LBP covers a spectrum of different types of pain that frequently overlap with a variable and multifactorial etiology. The prevalence and incidence of LBP ranged from 1.4 to 20.0% and 0.024–7.0% and despite several peer-reviewed published studies, there is little consensus regarding its epidemiology and its risk factors [4]. Beyond taxonomic aspects in LBP the poor correlation with pathology and symptoms is evident and highlight how pain is distinct from nociception. Many others context-dependent emotional, cognitive, and behavioral elements are involved [6]. Surgical approach stays mandatory in case of neurological deficit, progressive foot droop and paralyzing sciatica. Treatment should generally begin with conservative methods. In case of failure, between minimally invasive techniques, results support percutaneous paravertebral oxygen-ozone injections as one of the most common and effective procedures in reducing pain and improving functional status of LBP patients. Ozone might exert its action in reducing LBP with a coupled mechanical and anti-inflammatory effect. In peri-radicular probably normalize nerve function by a eutrophic effect that improves perineural microcirculation reducing local hypoxia due to both arterial compression and venous stasis in paraspinal musculature act as anti-inflammatory and myorelaxant with a therapeutic effect also on trigger points [39, 40]. Most of authors are agree considering ozone therapy a safe procedure.

In literature have been reported complications but most are related to malpractice and/or without a causal relationship between the ozone administration and the adverse event. Often those who report or analyze a complication is not who have performed or have knowledge of the procedure. Precision in ozone concentration is nowadays warranted by modern medical ozone generators with CE marking and consequently application of some European Directives that are mandatory to certify the conformity of the product to these directives in the responsibility of the manufacturer. Ozone Therapy is a medical act, therefore is fundamental the fully respect of good clinical practices or guidelines as suggest by World Federation of Oxygen Ozone Therapy and others Scientific Societies recognized by the Ministry of Health (Law n.24/2017). All this with specifically regard to Volumes, Concentrations, Indications, Timing of Treatments.

In the Systematic Reviews the treatment protocols are characterized from a lack of standardization that makes difficult to compare results and not allowing to get high quality conclusions or recommendations.

Anatomic landmark palpation-guided injections (ALMPG) have long been part of the treatment for arthritis and soft tissue rheumatism among musculoskeletal providers. Ultrasound-guided (USG) injections have been shown to be more accurate and less painful than ALMPG injections and increases procedural safety to allow for additional procedures at the point-of-care that previously have had not been considered (e.g., hip joint injection). With specifically regard to out-clinical settings, the development of ultrasound has certainly increased precision on the target by increasing efficiency and therapeutic effect.

Switching from a concept of interbody block to peri radicular injection could elevate the effectiveness of procedure, deeper injection ultrasound guided or assisted of the gaseous mixture could reach in a better way the nerve radix without the risk of an intra-foraminal or discal approach procedures that requires specifically clinical setting. Ultrasounds provide a real-time dynamic tissue assessment identifying the target region, confirming placement of the needle at the appropriate location thereby minimizing risks of injury to adjacent structures, and ensuring correct localization of therapeutic agent. In the last decades image quality has greatly improved and the machines have become portable, relatively inexpensive, and simple to use with a shorter learning curve. Searching in literature, ...” ultrasound guidance in Paravertebral Injections of Ozone.”, up to the present, we found only studies with small sample size. The need to improve safety of infiltration technique has led to consider the zygapophyseal articular plane’s as structure sufficiently close to the root and at the same time involved in the axial load. Infiltrating deeper and closest to the target allows smaller volume of O2/O3. Discomfort, heaviness, burning, vasovagal reaction (related to large volume injected) may compromise the continuity of treatment and patient’s confidence in the procedure.

Facet-Joints are true synovial joints involved in load bearing of an axial compression and therefore possible pain generators. Each one receives innervation by the medial branch of the dorsal ramus of the nerves the same level and above. There are few conditions in interventional pain medicine as controversial as lumbar facet joint pain. Regarding prevalence, the cited frequency of lumbar facet joint pain ranges from as low as 4.8% to over 50%. The wide disparity in reported prevalence raises questions regarding the accuracy of diagnostic testing in the absence of any non-interventional diagnostic reference standard. There is poor correlation between facet joint pathology on imaging and LBP. Can be posited that the technological limitations of US and individual patient factors (BMI, Adipose tissue distribution) are key contributors to the lower accuracy of US-guided MBB and FJI. On the other hand, the use of US may also be considered when diagnostic accuracy is a secondary concern. As suggested by the findings of the meta-analysis of Wu et al.68, the therapeutic effects of US-guided FJI may not be affected by inaccurate needle placement; thus, US may be an acceptable imaging modality for these injections. From the perspective view of physical medicine and rehabilitation, both needle and gas have a role in eliciting a complex series of chemical and neurological reactions leading to the disappearance of pain in many patients with LBP (also called “chemical acupuncture”). In fact, ozone, acts on chronic pain as a reflex therapy. Pre-procedure assessment, measurements as Skin Muscle distance and Skin-Lamina distance (corresponding to maximum paravertebral muscles depth), post-procedure valuation of the Oxygen-Ozone distribution in the tissues; may be an added value to improve procedural ac-

curacy and optimize clinical outcomes. In a cohort study of 56 patients (mostly focused on sciatica pain control by peri radicular ultrasound infiltrations), authors documented a significant improvement in radiating pain, reduction of kinesiophobia while modest were the patient perception of quality of life evaluated by SF 12. This study suffers from several limitations: retrospective design and lack of a control group to compare outcomes of peri radicular OOT. Furthermore, the follow-up period is just six months, and therefore it was not possible to assess the long-term effects of the treatment.

Large part of studies does not evaluate outcomes with homogeneous assessment methods; therefore, it is hard to make comparisons or draw conclusions. Often are used scales more suited to acute than chronic pain situations, as VAS or NRS.

LBP should be evaluated with specifically tool exploring both pain interference and functioning. Roland Morris Disability Questionnaire (RMDQ), Oswestry Disability Index (ODI), and Quebec Back Pain Disability Scale (QBPDS) the most suited scales [72, 73].

Another problem, as cited before, was lack of standardization in the treatment protocols providing different doses, timing, length of follow up or criteria to qualify no responders. Other limitations were the lack of precise diagnosis and the frequent use of mixed therapeutic strategies, thus negatively affecting the possibility of evaluating the sole ozone contribution to the clinical outcome.

The analysis of literature revealed overall poor methodologic quality, with most studies flawed by relevant bias, therefore additional studies with adequate and consistent methodologies are needed and longer follow-up periods to clarify the efficacy of this intervention.

All these limits, now, do not allow to establish a solid level of evidence to recommend as a routine intervention in individual with low back pain even though superiority of OOT vs systemic drugs and local corticosteroids has been demonstrated in the short as well as in the medium term.

This systematic review conducted by Sconza39 in 2021 and published on the European Review for Medical and Pharmacological Sciences conclude affirming that OOT represents a promising approach for LBP, with a good safety profile and therapeutic potential, and it could be included among armamentarium of the conservative management of this common condition. Nonetheless, the current paucity of high-quality trials warrants further studies to elucidate some fundamental issues regarding the optimal therapeutic protocols, the number of injections, dosages, and site of administration (for example paravertebral vs peri-radicular).

Conclusion

Low back pain (LBP) is the leading cause of disability worldwide. Various approaches to diagnose and manage LBP have arisen, leading to an exponential increase in health care costs. Paradoxically, this trend has been associated with a concurrent increase in disability and chronicity. Growing evidence suggests that current practice is discordant with contemporary evidence and is in fact often exacerbating the problem. Change will demand a cultural shift in LBP beliefs and practice [74]. Pain is a multidimensional experience in an individual context. Ozone therapy is an adjunctive therapy and should be performed along with and not instead of the allopathic medicine. The application of ozone therapy complements other allopathic treatments such pharmaceutical interventions and surgical procedures and does not replace them as an alternative. From this point of view ozone represents a safety complementary approach when applied with respect to good clinical practices proposed from World Federation of Ozone Therapy or other Scientific Society. Ozone therapy is a medical act therefore the patient must be well evaluated beyond the symptom to consider the improvement not only in pain perception but also in functional terms. With specifically regard to LBP (associated or not to radicular pain), OOT has showed analogue or also more efficacy than other treatments like systemic drugs or local steroids injections. Data are not conclusive for studies with moderate to high risk of bias. In this scenario, O2O3 therapy remains a promising conservative and minimally invasive intervention that improves pain symptoms and patients' quality of life. Outcomes could be optimized performing infiltrations with an anatomical view of the area and better performances. In a metanalysis that compared the effectiveness of low back pain treatment with oxygen-ozone mixture between image-guided and non-image- guided percutaneous injection techniques no consensus was reached despite better therapeutic performance with higher impact on pain reduction and lower-aged, related variability [33]. Further studies are still required to assess the superiority of this method compared to conventional surgery and different mini-invasive techniques both in terms of efficacy and results' stability over time. Evidence is low mainly for the lack of studies with adequate and consistent methodologies. We need studies with homogeneous criteria for recruitment, treatment, and evaluation on larger statistical samples with adequate follow-up periods to establish efficacy over time.

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