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CONTENTS

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Basic Science Research

INFLUENCE OF HYALURONIC ACID ON EXTRACELLULAR MATRIX PRODUCED BY MESENCHYMAL STEM CELLS

L. Scapoli[1], A. Avantaggiato[2], A.G.A. Khater[3]

[1]Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Italy
[2]Private Practice, Codigoro, Ferrara, Italy
[3]Faculty of Oral and Dental Medicine, Ahram Canadian University, Egypt

Correspondence to:
Luca Scapoli, PhD,
Department of Experimental, Diagnostic and Specialty Medicine,
University of Bologna, Bologna, Italy
e-mail: luca.scapoli2@unibo.it

ABSTRACT

Hyaluronic acid is a natural component of the extracellular matrix found in various body fluids, organs and tissues. It is widely used in tissue engineering, as a drug delivery system and in various medical and pharmaceutical applications. It plays an important role in supporting cells during wound healing, recognizing specific surface receptors during the healing process, and favoring collagen deposition and angiogenesis. Hyaluronic acid is known to activate stem cells and is involved during the differentiation process. Nevertheless, it was demonstrated as hyaluronic acid's biological functions and properties are strictly dependent on its molecular weight, also showing opposite effects between high-molecular-weight and low-molecular-weight.

Here we tested the effects of hyaluronic acid with different molecular weights on mesenchymal stem cells, assessing the role of this natural linear polysaccharide in extracellular matrix deposition and remodeling.

Gene expression of genes belonging to the "Extracellular Matrix and Adhesion Molecules" pathway was investigated in mesenchymal stem cells treated with high, medium, and low molecular weight hyaluronic acid solution 10 mg/ml for 24 h.

Hyaluronic acid promotes the synthesis and stabilization of the extracellular matrix. Furthermore, treated cells respond to the treatment by opposing the inflammatory action of the molecule by down-regulating numerous metalloproteinases, thus trying to stop the degeneration processes of the extracellular matrix.

KEYWORDS: *mesenchymal stem cells, extracellular matrix, hyaluronic acid, gene expression, Real-Time PCR*

INTRODUCTION

Hyaluronic acid (HA) is an acidic, non-sulfated glycosaminoglycan with a repeating disaccharide structure of

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D-glucuronic acid and N-acetyl-D-glucosamine. These simple dimers form long linear polymer chains counting thousands of repetitions and a molecular weight ranging up to 10 MDa (1). HA is a component of bacterial, fungal, extracellular matrix with biocompatible and biodegradable properties. HA is considered a promising material for tissue engineering. HA general biological functions are hydration, space-filling capacity and lubrification.

It was demonstrated as HA's biological functions and properties are strictly dependent on its molecular weight, also showing opposite effects between high-molecular-weight (HMW, if $>10^6$ Da) and low-molecular-weight (LMW, if $\leq 10^6$ Da) (2). HA is a major constituent of the extracellular matrix; it is constantly synthesized as high molecular weight and is degraded very fast by hyaluronidases in low molecular weight (3). Moreover, it plays an important role in supporting cells during wound healing (4), recognizing specific surface receptors during the healing process, and favoring collagen deposition and angiogenesis. HA is known to activate stem cells and is involved during the differentiation process. However, HA is rapidly metabolized, and its half-life is less than a day. HA is also actively degraded within 24 h by the hyaluronidase enzymes or by reactive oxygen species (4).

One of the cell types related to HA materials for tissue engineering are stem cells derived from dental pulp (DPSC). Based on their multilineage differentiation potential, high proliferation activity, and self-renewal, DPSC are considered an auspicious mesenchymal cell population for cell-based therapy and tissue regeneration (5). The dental pulp is an attractive alternative source of mesenchymal stem cells due to simple access (5). DPSC can be obtained from an extracted tooth, most often third lower molar, as part of planned treatment; in fact, after extraction, these teeth are considered biological waste and discarded. Isolation of the dental pulp is not considered an overtreatment, since third molar is extracted for other reasons (6). The capability of DPSC of differentiating into various cell types, such as odontoblasts, osteoblasts, chondroblasts, endothelial cells, and neural cells, indicates their possible application in the fields of regenerative medicine and tissue engineering.

Several findings identify HA as non-toxic material that does not negatively affect viability, proliferation activity, or differentiation potential of DPSC (7). Additional authors present gene expression changes in DPSC after being exposed to HA, while only a few reports investigate the effect of HA on DPSC surface markers (8, 9). These studies do not assess the biological properties of discrete HA fractions of different sizes; so, no one conclusion can be found about the influence of HA molecules of different weights on DPSC properties.

Here we tested the effects of HA with different molecular weight on DPSC, assessing the role of this natural linear polysaccharide in extracellular matrix deposition and remodeling.

MATERIALS AND METHODS

Dental pulp stem cell isolation and viability, HA treatment, RNA isolation, reverse transcription and quantitative real-time RT-PCR were extensively described elsewhere (9).

In summary, dental germ pulp was extracted from the third molars of healthy subjects. The pulp was digested, and the solution was then filtered. Filtered cells were cultivated in an α-MEM culture medium and the purity of dental pulp stem cells (DPSC) cultures was determined by means of flow cytometric analyses with specific antibodies. A cell viability test was performed to test the optimal HA concentration to be added to cell cultures. After treatment, cells were trypsinized and processed for RNA extraction. Custom primers belonging to the "Extracellular Matrix and Adhesion Molecules" pathway were purchased from Sigma Aldrich. The selected genes grouped by functional pathway are listed in Table I. Reverse transcription and quantitative real-time RT-PCR were performed and a statistical analysis using the delta/delta Ct calculation method (10).

RESULTS

The right concentration of hyaluronic acid (high, medium and low molecular weight) to be used in the treatment of DPSC cultured *in vitro*, were established by making serial dilutions of the stock solutions and treating the cells for 24 hours. Cell viability was measured using the PrestoBlue ™ assay and it was established that the optimal concentration of the treatment that did not significantly affect cell viability was 10 mg/ml for all three types of hyaluronic acid.

Gene expression of genes belonging to the "Extracellular Matrix and Adhesion Molecules" pathway was investigated in DPSC treated with high, medium and low molecular weight hyaluronic acid solution 10 mg/ml for 24 h.

Table II show significant gene expression levels after 24h of treatment with high molecular weight hyaluronic acid

Table I. *Selected genes tested in real-time PCR grouped by functional pathway.*

Pathway	Gene symbol	Gene name
Collagens & Extracellular Matrix Structural constituent	COL1A2	collagen type I alpha 2 chain
	COL2A1	collagen type II alpha 1 chain
	COL3A1	collagen type III alpha 1 chain
	COL4A1	collagen type IV alpha 1 chain
	COL5A1	collagen type V alpha 1 chain
	COL6A1	collagen type VI alpha 1 chain
	COL7A1	collagen type VII alpha 1 chain
	COL8A1	collagen type VIII alpha 1 chain
	COL9A1	collagen type IX alpha 1 chain
	COL10A1	collagen type X alpha 1 chain
	COL11A1	collagen type XI alpha 1 chain
Cell Adhesion Molecule	CCTNA1	catenin alpha 1
	CTNNB	catenin beta 1
	CTNND2	catenin delta 2
	VCAN	versican
Transmembrane Receptor	HAS1	hyaluronan synthase 1
	ILF3	interleukin enhancer binding factor 3
	ITGA1	integrin subunit alpha 1
	ITGA2	integrin subunit alpha 2
	ITGA3	integrin subunit alpha 3
	ITGA4	integrin subunit alpha 4
	ITGA5	integrin subunit alpha 5
	ITGA6	integrin subunit alpha 6
	ITGA7	integrin subunit alpha 7
	ITGA8	integrin subunit alpha 8
	ITGB1	integrin subunit beta 1
	ITGB2	integrin subunit beta 2
	ITGB4	integrin subunit beta 4
	ITGB5	integrin subunit beta 5
	LAMA1	laminin subunit alpha 1
	LAMA2	laminin subunit alpha 2
	LAMA3	laminin subunit alpha 3
	LAMB1	laminin subunit beta 1
	LAMB2	laminin subunit beta 2
	LAMB3	laminin subunit beta 3
Extracellular Matrix Protease	MMP2	matrix metallopeptidase 2
	MMP7	matrix metallopeptidase 7
	MMP8	matrix metallopeptidase 8
	MMP9	matrix metallopeptidase 9
	MMP10	matrix metallopeptidase 10
	MMP11	matrix metallopeptidase 11
	MMP12	matrix metallopeptidase 12
	MMP13	matrix metallopeptidase 13
	MMP14	matrix metallopeptidase 14
	MMP15	matrix metallopeptidase 15
	MMP16	matrix metallopeptidase 16
	MMP24	matrix metallopeptidase 24
	MMP26	matrix metallopeptidase 26
TGFβ Signaling	TGFB1	transforming growth factor beta 1
	TGFB2	transforming growth factor beta 2
	TGFB3	transforming growth factor beta 3
Extracellular Matrix Protease Inhibitor	TIMP1	TIMP metallopeptidase inhibitor 1
Housekeeping gene	RPL13	ribosomal protein L13

Table II. *Significant gene expression levels after 24h treatment with HMW-HA, as compared with untreated cells.*

Gene	Fold change	SD (+/-)	Gene function
COL2A1	0.22	0.01	Collagens & Extracellular Matrix Structural constituent
COL5A1	0.32	0.02	Collagens & Extracellular Matrix Structural constituent
COL7A1	0.19	0.01	Collagens & Extracellular Matrix Structural constituent
COL8A1	0.09	0.02	Collagens & Extracellular Matrix Structural constituent
COL11A1	0.37	0.03	Collagens & Extracellular Matrix Structural constituent
CTNND2	0.23	0.01	Cell Adhesion Molecule
VCAN	0.13	0.02	Cell Adhesion Molecule
HAS1	0.24	0.00	Transmembrane Receptor
ITGA4	0.38	0.01	Transmembrane Receptor
ITGA7	0.26	0.06	Transmembrane Receptor
ITGA8	0.09	0.00	Transmembrane Receptor
LAMA1	0.44	0.02	Transmembrane Receptor
LAMB2	0.48	0.00	Transmembrane Receptor
MMP2	0.44	0.05	Extracellular Matrix Protease
MMP7	0.49	0.14	Extracellular Matrix Protease
MMP8	0.13	0.01	Extracellular Matrix Protease
MMP10	0.05	0.00	Extracellular Matrix Protease
MMP11	0.09	0.01	Extracellular Matrix Protease
MMP12	0.20	0.02	Extracellular Matrix Protease
MMP14	0.17	0.01	Extracellular Matrix Protease
MMP15	0.19	0.04	Extracellular Matrix Protease
MMP16	0.24	0.01	Extracellular Matrix Protease
MMP24	0.31	0.02	Extracellular Matrix Protease
MMP26	0.29	0.03	Extracellular Matrix Protease
TGFB1	0.35	0.04	TGFβ Signaling
TGFB3	0.39	0.01	TGFβ Signaling
TIMP1	0.45	0.01	Extracellular Matrix Protease Inhibitor

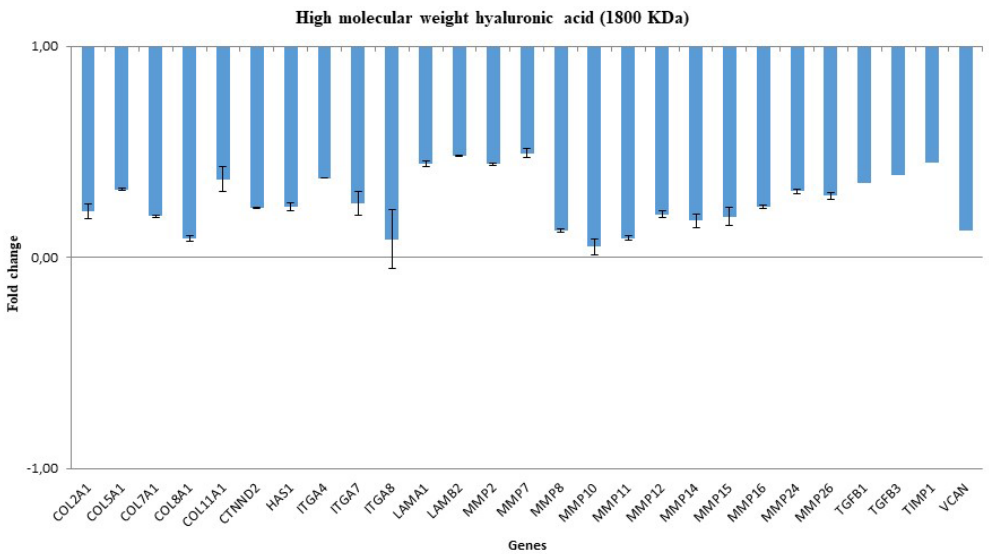

Fig. 1. *Gene expression profile of human DPSC treated with HMW-HA 10 mg/ml.*

(HMW-HA), as compared with untreated cells. All the significant gene were down-regulated in treated cells. Genes belongs to "Collagens & Extracellular Matrix Structural constituent" (COL2A1, COL5A1, COL7A1, COL8A1, COL11A1), "Cell Adhesion Molecule" (CTNND2, VCAN), "Transmembrane Receptor" (HAS1, ITGA4, ITGA7, ITGA8, LAMA1, LAMB2), "Extracellular matrix protease pathway" (MMP2, MMP7, MMP8, MMP10, MMP11, MMP12, MMP14, MMP15, MMP16, MMP24, MMP26), TGFβ Signaling (TGFB1, TGFB3) and "Extracellular Matrix Protease Inhibitor" (TIMP1). Fig. 1. represents the gene expression profile of treated DPSC compared with control (untreated cells).

Table III reports the significant gene expression levels after 24h treatment with medium molecular weight hyaluronic

Table III. *Significant gene expression levels after 24h treatment with MMW-HA, as compared with untreated cells.*

Gene	Fold change	SD (+/-)	Gene function
COL1A2	0.42	0.08	Collagens & Extracellular Matrix Structural constituent
COL2A1	0.12	0.03	Collagens & Extracellular Matrix Structural constituent
COL4A1	0.32	0.01	Collagens & Extracellular Matrix Structural constituent
COL5A1	0.27	0.01	Collagens & Extracellular Matrix Structural constituent
COL6A1	0.40	0.04	Collagens & Extracellular Matrix Structural constituent
COL7A1	0.11	0.01	Collagens & Extracellular Matrix Structural constituent
COL8A1	0.26	0.02	Collagens & Extracellular Matrix Structural constituent
COL9A1	0.21	0.03	Collagens & Extracellular Matrix Structural constituent
CTNNA1	0.43	0.02	Cell Adhesion Molecule
CTNNB	0.43	0.01	Cell Adhesion Molecule
CTNND2	0.21	0.05	Cell Adhesion Molecule
HAS1	0.32	0.02	Transmembrane Receptor
ILF3	0.42	0.05	Transmembrane Receptor
ITGA3	0.38	0.01	Transmembrane Receptor
ITGA4	0.29	0.04	Transmembrane Receptor
ITGA7	0.23	0.03	Transmembrane Receptor
ITGA8	0.14	0.03	Transmembrane Receptor
ITGB1	0.40	0.02	Transmembrane Receptor
ITGB2	0.49	0.02	Transmembrane Receptor
ITGB5	0.38	0.03	Transmembrane Receptor
LAMA1	0.14	0.00	Basement Membrane Constituent
LAMA2	0.24	0.00	Basement Membrane Constituent
LAMB1	0.35	0.10	Basement Membrane Constituent
LAMB2	0.30	0.00	Basement Membrane Constituent
LAMB3	0.34	0.01	Basement Membrane Constituent
MMP2	0.18	0.00	Extracellular Matrix Protease
MMP7	0.36	0.01	Extracellular Matrix Protease
MMP8	0.10	0.01	Extracellular Matrix Protease
MMP9	0.27	0.08	Extracellular Matrix Protease
MMP10	0.02	0.00	Extracellular Matrix Protease
MMP11	0.16	0.01	Extracellular Matrix Protease
MMP13	2.25	0.50	Extracellular Matrix Protease
MMP16	0.26	0.02	Extracellular Matrix Protease
MMP24	0.37	0.05	Extracellular Matrix Protease
MMP26	0.19	0.05	Extracellular Matrix Protease

acid (MMW-HA) compared to untreated cells. Genes differentially expressed were "Collagens & Extracellular Matrix Structural constituent" (COL1A2, COL2A1, COL4A1, COL5A1, COL6A1, COL7A1, COL8A1, COL9A1), "Cell Adhesion Molecule" (CTNNA1, CTNNB, CTNND2), "Transmembrane Receptor" (HAS1, ILF3, ITGA3, ITGA4, ITGA7, ITGA8, ITGB1, ITGB2, ITGB5), "Basement Membrane Constituent" (LAMA1, LAMA2, LAMB1, LAMB2, LAMB3) and "Extracellular Matrix Protease" (MMP2, MMP7, MMP8, MMP9, MMP10, MMP11, MMP13, MMP16, MMP24, MMP26). All the genes were significantly down-regulated except MMP13.

Fig. 2 shows the expression profile of genes up-and down-regulated in treated stem cells with medium molecular weight hyaluronic acid. Table IV reports the significant gene expression levels after 24h treatment with low molecular weight hyaluronic acid (LMW-HA) compared to untreated cells. The treatment induces the down-regulation of genes belonging to "Collagens & Extracellular Matrix Structural constituent" (COL10A1), "Transmembrane Receptor" (ITGA2, ITGB2), "Basement Membrane Constituent" (LAMA2, LAMB1), "Extracellular Matrix Protease" (MMP8, MMP10, MMP11, MMP24, MMP26). Only the "Basement Membrane Constituent" LAMB 1 was up-regulated, as shown in Fig. 3.

DISCUSSION

HA is a natural extracellular matrix component found in various body fluids, organs, and tissues (11). It is a molecule widely used in tissue engineering, as a drug delivery system, and in various medical and pharmaceutical applications (12, 13). HA is, in fact, able to favor the formation of a temporary structure useful for the deposition of proteins belonging to the extracellular matrix. It has been widely demonstrated to promote cell adhesion, proliferation, and migration (14). Furthermore, it is involved in maintaining the efficiency of the extracellular matrix and tissue hydration.

Here we tested the effects of HA with different molecular weights on DPSC, assessing the role of this natural linear polysaccharide in extracellular matrix deposition and remodeling.

Gene expression of genes belonging to the "Extracellular Matrix and Adhesion Molecules" pathway was investigated in DPSC treated with high, medium, and low molecular weight hyaluronic acid solution 10 mg/ml for 24 h. DPSC treated with HMW-HA showed a high number of down-regulated metallopeptidases, which normally have the function of degrading the extracellular matrix.

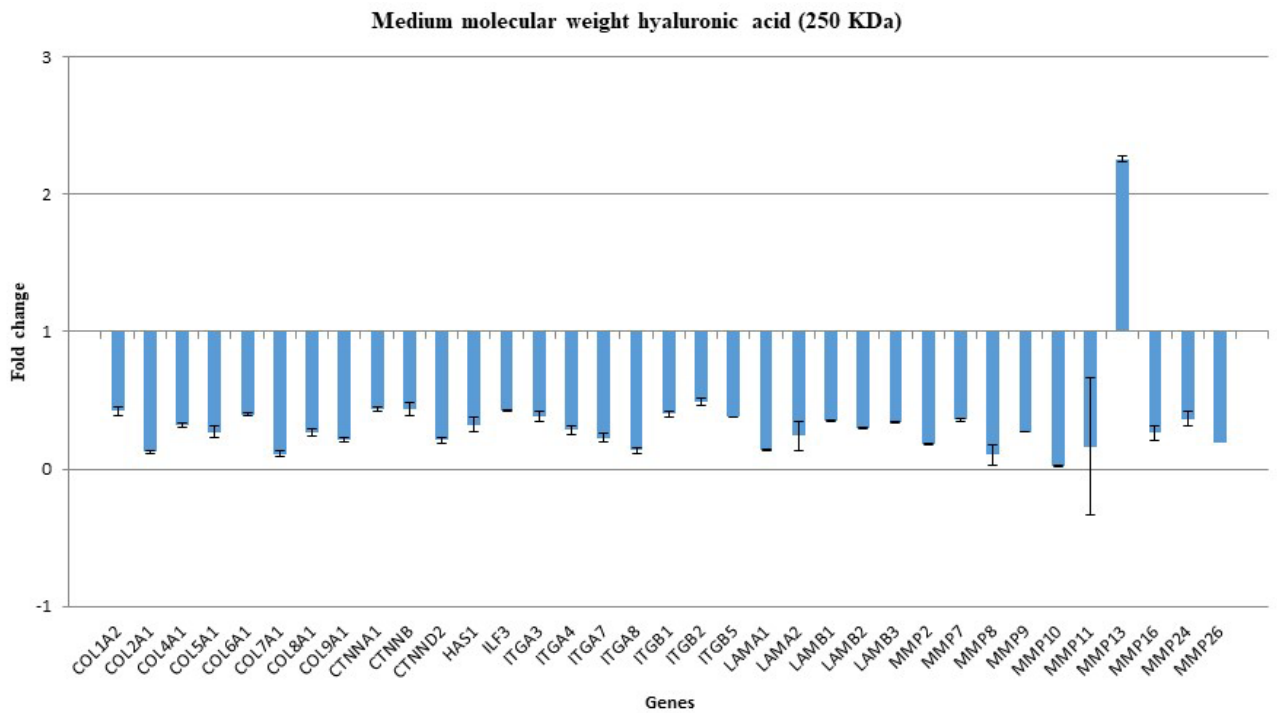

Fig. 2. *Gene expression profile of human DPSC treated with MMW-HA 10 mg/ml.*

COL11A1 is a gene involved in reorganizing collagen fibrils in the extracellular matrix. COL11A1 is up-regulated in head and neck carcinomas, while its expression does not vary in normal tissue (15). Several other tumors show high levels of gene expression (16, 17). COL11A1 expression is progressively higher from early lesions to advanced stages of the disease, highlighting its importance and association with tumor aggression, progression, and metastization. Therefore, it would seem that this gene is involved in the epithelium-mesenchymal transition and the degradation of the extracellular matrix. Small fragments of HA are potent pro-inflammatory and proangiogenic molecules and play a crucial role in cancer progression (18). HMW-HA seems to promote the synthesis and stabilization of the extracellular matrix by down-regulating COL11A1.

HAS1 and HAS2 are responsible for producing high molecular weight hyaluronic acid molecules (19). In stem cells treated with HMW-HA, the HAS1 enzyme is under-expressed due to the administration of exogenous hyaluronic acid. For the same reason, other genes such as TGFB1 and TGFB3 involved in the synthesis of HMW-HA are down-regulated compared to untreated cells.

Table IV. *Significant gene expression levels after 24h treatment with LMW-HA, as compared with untreated cells.*

Gene	Fold change	SD (+/-)	Gene function
COL10A1	0.20	0.03	Collagens & Extracellular Matrix Structural constituent
ITGA2	0.26	0.03	Transmembrane Receptor
ITGB2	0.47	0.16	Transmembrane Receptor
LAMA2	0.14	0.01	Basement Membrane Constituent
LAMB1	6.74	1.34	Basement Membrane Constituent
MMP8	0.37	0.00	Extracellular Matrix Protease
MMP10	0.05	0.01	Extracellular Matrix Protease
MMP11	0.23	0.05	Extracellular Matrix Protease
MMP24	0.40	0.06	Extracellular Matrix Protease
MMP26	0.44	0.00	Extracellular Matrix Protease

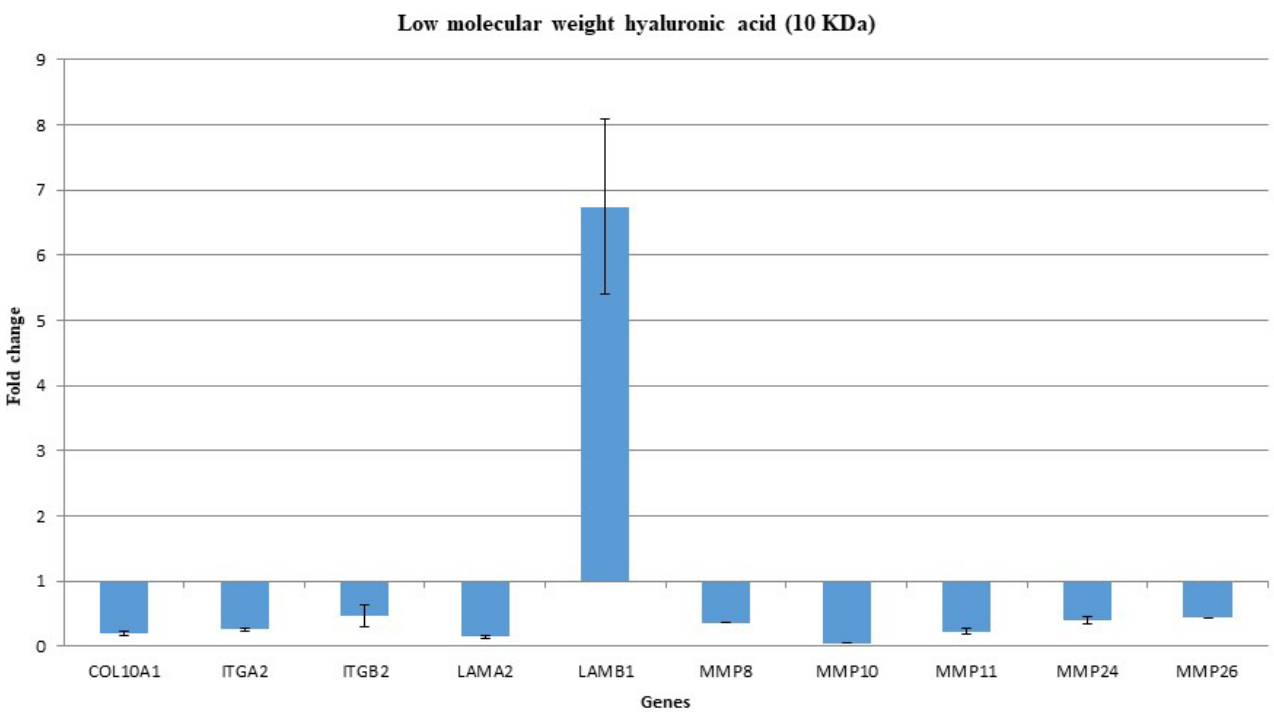

Fig. 3. *Gene expression profile of DPSC treated with LMW-HA 10 mg/ml.*

Low molecular weight hyaluronic acid (LMW-HA) is involved in tissue inflammation mechanisms (19, 20). In DPSC treated with this molecule, it would seem that cells respond to the treatment by opposing the inflammatory action of the molecule by down-regulating numerous metalloproteinases, thus trying to stop the degeneration processes of the extracellular matrix.

The results indicate that high and low molecular weight hyaluronic acid influences the remodeling of the extracellular matrix deposited by mesenchymal stem cells. However, other data are necessary to understand these effects better, increasing the exposure times of the treatments in order to verify the effects of this biopolymer on the deposition of the extracellular matrix.

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Review

DENTINOGENESIS IMPERFECTA: A REVIEW

F. Carinci

Department of Translational Medicine, University of Ferrara, Ferrara, Italy

Correspondence to:
Francesco Carinci, MD
Dept of Translational Medicine, University of Ferrara, Ferrara, Italy
e-mail: crc@unife.it

ABSTRACT

Dentinogenesis imperfecta (DGI) is an inherited dentin disease resulting in fragile teeth that affect the primary and permanent dentitions. It causes physical and aesthetic problems, including tooth discoloration and staining, and is responsible for great damage and wear to the entire dentition. DGI is classified into three types, with COL1A1 and COL1A2 gene mutations present in the first type, and mutations of the DSPP gene present in the second and third types. Treatment is focused on the restoration and replacement of damaged and worn teeth, as well as aesthetic improvements. Restorative, prosthodontic, and orthodontic treatment is often necessary. The aim of this paper is to shed light on this pathological disease and the importance of obtaining an early diagnosis which is necessary to implement treatment.

KEYWORDS: *DGI, dentin defect, dental, musculoskeletal*

INTRODUCTION

Dentinogenesis imperfecta (DGI) is an autosomal dominant inherited dentin disorder that affects both the primary and permanent dentitions. It causes physical and aesthetic problems, including opalescent dentin, brown or blue-hued tooth discoloration and staining, and is a common genetic dentin defect, estimated to affect 1 in 8,000 people (1).

A brief look at the history of DGI shows that it may have been first identified in 1882 by Barret, and that the enamel deformity occurring in the disorder was first described in literature in 1971 (2).

DGI was originally classified in three types in 1973 by Shields; these being Type I, II and III (3). These are continued to be referenced today, as well as a newer, revised system of two types.

This review outlines the current literature on DGI with a summary of the clinical characteristics, the classification of the disorder into subgroups, and the standard treatment options. Because of the serious physical and aesthetic problems associated with the disorder, an early diagnosis is vital.

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Clinical description

DGI is an autosomal dominant disease consisting of dentin defects, altered dentin mineralization and limited root dentin. The teeth are made up of four different tissues, which include the dentin, enamel, cementum, and pulp. The teeth are mostly composed of dentin, which is softer than enamel (4). This dentin is altered in people with DGI.

DGI is characterized by opalescent dentin, a characteristic discoloration and staining of the teeth, enamel loss, tooth weakening and erosion, bulbous crowns, cervical restriction, short roots, and destructed root canals and pulp chambers (5). Clinical severity of the disease is variable and can range from mild to very severe (6).

Crown discoloration is a pronounced characteristic, and can present with grey, bluish-grey, and amber-brown tinges (7). Teeth present with a translucent, opalescent quality. These aspects are aesthetically displeasing and can cause phycological distress for the patients.

Structurally, the teeth are very delicate and wear easily. Enamel damage, chipping and crown destruction can present, and the crowns themselves may appear as bulbous or domical and smaller than usual (8). Cervical restriction due to the erosion of the hard tissues around the neck of the teeth may also be noted. The roots are shortened, and canals and pulp chambers can be destructed or obliterated (9).

Diagnosis of DGI is usually obtained through clinical examination, radiography, and assessments of family history, and genetic counseling can be confirmative.

A case revision was presented by de La Dure-Molla which compared the severity of clinical features between the primary and permanent dentitions. This showed that milder symptoms occurred in the cases of the permanent teeth, with milder and severe symptoms presenting in the cases of the primary teeth (10).

Classification

DGI was classified into three types by Shields. All three types are inherited genetic disorders, but the responsible genes vary.

Type I DGI is associated with osteogenesis imperfecta, a congenital disorder linked to mutations of the COL1A1 or COL1A2 genes, that leads to brittle bones and skeletal irregularities. Oral hygiene is affected with tooth loss being common. Between 20 and 40 percent of people suffering from osteogenesis imperfecta may have Type I DGI (11).

Dentin sialophosphoprotein (DSPP) gene mutations are present in DGI Types II and III. The DSPP gene encodes proteins that create the dentin extracellular matrix, which include collagen type I and the non-collagenous proteins responsible for DGI such as dentin sialoprotein (DSP), dentin glycoprotein (DGP) and dentin phosphoprotein (DPP) (12). Mutations of the DSPP gene alter the dentin-producing proteins and are responsible for the dentin defects of the disorder.

Type II DGI, the most common DGI type, shares the same clinical characteristics of Type I, however the distinguishing factor is that it is not associated with osteogenesis imperfecta (13).

Type III DGI is a rare and severe form, associated with a specific U.S. population of Brandywine, located in Southern Maryland near Washington, DC (14). In Type III DGI there is rapid erosion and damage to teeth, with the possibility of dental pulp becoming exposed (15).

Shield's classification of DGI into these three types was clinically based and is still relevant today, however recent genetic research by de La Dure-Molla has shown that the three types are a variation of the same disease, and therefore a revised classification system was created that divides the diseases into two groups of DGI types II and III (10).

Treatment

Early diagnosis of DGI is vital to initiate proper treatment, as the problematic dentin formation of DGI that leads to tooth erosion and fractures, and the destruction can progress quickly, eventually requiring corrective dental procedures (16). Treatment follows a multidisciplinary strategy that depends on the patient's age and severity of the disease (17). Restorative, prosthodontic, and orthodontic treatment is often necessary (18). Improving the aesthetic features of patients is also of great importance in regard to the patient's self-image and oral health-related quality of life (19).

Treatment usually begins with the primary teeth with fillings or crowns. Dental implants and dentures are standard for permanent dentition when replacement becomes the primary option. Orthodontic treatment including removable appliances, functional appliances, and fixed appliances, can be a long process and may require years of treatment, which can result in frustration and difficulty for the patient (20).

Dental implants may have limited success, as they require a solid tooth base to adhere to which may be absent with the damage caused by DGI. There is a risk of implant failure.

Porcelain fused to metal (PFM) crowns and bridges, veneers, as well as stainless steel, composite and all-ceramic crowns are used to treat DGI. Caries are common and pose a great risk of failure for restorations. Therefore, impeccable oral hygiene is of great importance and the patient must commit to this, even in the face of tooth pain and sensitivity (21).

In Type I bisphosphonates are sometimes prescribed to treat the bone problems of the accompanying disorder osteogenesis imperfecta. While these bisphosphonates improve bone qualities, they can negatively impact the oral restoration process (22).

CONCLUSION

Although DGI may not be a prominent hereditary disorder overall, it is the most common genetic dentinal disease. The attrition and destruction to dentition, as well as the aesthetic impacts of discoloration and staining, can have a severe, negative impact on the patient's life. The oral quality of life is greatly affected, and subsequent dental restorations and replacement may demand an extensive amount of time and commitment on the end of the patient. Dental anxiety may form as a result. The patient may also suffer with poor self-image and experience negative social aspects resulting from the aesthetic qualities of their teeth.

Progress can be made by further investigation into the genetic basis of DGI and the classification of the subtypes, important research for early diagnosis and subsequent treatment.

Conflicts of Interest:

The authors declare no conflict of interest.

Author Contribution:

The author has read and agreed to the published version of the manuscript.

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Review

GENDER AND SOCIO-ECONOMIC ISSUES IN THE CLINICAL ASSESSMENT OF ORTHOPAEDIC PATIENTS DURING THE COVID-19 PANDEMIC

L. Moretti[1§], D. Bizzoca[2*§], E. Vitale[3], M. Delmedico[1], A. Spinarelli[1], A. Piazzolla[1], A. M. Moretti[4], B. Moretti[1], and G. Solarino[1]

[1]Orthopaedic and Trauma Unit - UOSD Vertebral Surgery, Department of Basic Medical Sciences, Neuroscience and Sense Organs, School of Medicine, University of Bari Aldo Moro, AOU Consorziale Policlinico, Bari, Italy;
[2]PhD course in Public Health, Clinical Medicine, and Oncology, University of Bari Aldo Moro, Bari, Italy;
[3]Mental Health Center in Modugno, Local Health Company;
[4] President of GISEG (Gruppo Italiano Salute e Genere)

**Correspondence:*
Davide Bizzoca MD,
UOSD Vertebral Surgery, AOU Consorziale Policlinico di Bari, Bari, Italy.
e-mail: da.bizzoca@gmail.com

[§]co-first authors

ABSTRACT

This observational study aims to depict the impact of gender and socio-economic issues on the health status of Italian Orthopaedic patients during the COVID-19 lockdown. An *Ad Hoc* questionnaire was developed and administered online. The following data were extracted from the questionnaire: age, body mass index (BMI), education level, distance from hospital, orthopaedic disease, concomitant medical comorbidities, living status (with/without cohabitants) and physical activity level (according to Tegner Activity Scale). The impact of the COVID-19 lockdown was studied by analysing differences related to the parameters mentioned above.

A significant increase in the call number to general practitioners and the orthopaedic surgeon was observed during the COVID lockdown, especially in patients with higher education levels. Reduced compliance in drug assumption was observed in patients with higher education levels during the lockdown (p=0.007). Almost all the analysed items were significantly influenced by the distance between the patient's domicile and the nearest hospital. However, no significant differences were observed comparing the pre-COVID to COVID lockdown.

Patients' gender and education level in the present study revealed a significant impact on their social behaviour during the COVID lockdown, compared with the pre-COVID period.

KEYWORDS: *Covid-19 perception, generaKe l well-being, orthopaedic patients, gender, pandemic, socio-economic issues*

INTRODUCTION

In late February 2020, a severe coronavirus disease 2019 (COVID-19) cluster was unexpectedly depicted in Northern Italy.

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The first autochthonous case of COVID-19 was diagnosed on February 20th in Codogno (Lodi, Lombardy). In the following 24 hours, thirty-six new COVID-19 cases, non-directly linked to Codogno Patient-1, were reported in Lombardy and Veneto.

The Italian Council of Ministers quickly put the two COVID-19 outbreak areas in quarantine, thus identifying the so-called "red zones". Nonetheless, the virus spread exponentially in Northern Italy and throughout the country in a few days.

Consequently, hospitals become overcrowded, several healthcare professionals become infected, and a dramatic increase in mortality rate among COVID-positive patients with comorbidities was depicted. Based on these findings, on March 9th, 2020, the Italian government released a new decree prohibiting travel and movement in public places, except for justifiable work reasons: the whole country was on lockdown.

This new scenario had an unpredictable impact on the mental status of COVID and non-COVID patients and healthcare professionals (1–3).

Previous studies have reported that the Severe Acute Respiratory Syndrome (SARS) epidemic and the H1N1 flu significantly impacted people's mental status (4, 5). Therefore, during the SARS outbreak, several studies investigated the psychological impact of the disease on the non-infected community (6-9). Older age, female gender and higher education were related to a higher fear of SARS contagion; for this reason, they used individual protective devices (10).

Currently, there is little information about gender and socio-economic differences in the perception of the COVID-19 pandemic. This study aims to depict the impact of gender and socio-economic issues on the health status of Italian Orthopaedic patients during the COVID-19 lockdown.

MATERIALS AND METHODS

A prospective multicentric observational study was performed. The study included all the Orthopaedic patients in Italy who were referred to the Orthopaedic emergency departments and Orthopaedic outpatient departments.

All the patients received an invitation to voluntary take part in the study. All the information collected had no diagnostic purposes, and the results were treated confidentially, guaranteeing complete anonymity. Each patient completed an online form provided by the Orthopaedic surgeons involved in this multicenter study; all the data were subsequently gathered in a unique anonym database.

An *Ad Hoc* questionnaire was developed and administered online. The following data were extracted from the questionnaire: age, body mass index (BMI), education level, distance from hospital, orthopaedic disease, concomitant medical comorbidities, living status (with/without cohabitants) and physical activity level (according to Tegner Activity Scale).

All the participants were also asked to describe their relationship with the general practitioner, the orthopaedic surgeon and the Emergency Department during the pre-COVID period (November 2019-January 2020) compared to the COVID lockdown period (March-April 2020) and compliance with drugs assumption and the local therapy (intra-articular injections, shock waves therapy, physiokinesis therapy) administration. The frequency of patients looking for information about their health condition on the internet and the fear of COVID-19 infection was also investigated.

The impact of the COVID-19 lockdown was studied by analysing differences related to gender, age, education level, distance from the hospital, number of medical comorbidities and living status.

Statistical analysis was performed using SPSS (version 20; IBM Corp, Armonk, NY). Descriptive statistics were used to evaluate the sample's demographic characteristics. The Chi-square test and Fisher's exact test were used to assess the variability between groups.

The Kruskal-Wallis test was performed to assess the variability between subgroups. The tests were two-tailed; statistical significance was set at $p<0.05$.

RESULTS

The primary data of the study are summarised in Table I. 782 patients completed the *Ad Hoc* questionnaire (male: 422; female:360; mean age: 59.77).

Table II shows gender- and age-related differences between the pre-COVID and COVID lockdown periods. No significant differences between genders and different age subgroups were depicted.

Table III summarises gender- and education-level-related differences between the pre-COVID and COVID lockdown periods. A significant increase in the call number to the general practitioner and the orthopaedic surgeon was observed during the COVID lockdown, especially in patients with higher education levels. Reduced compliance in drug assumption was observed in patients with higher education levels during the lockdown ($p=0.007$).

Table IV shows the results of the gender-specific analysis concerning patients' distance from the hospital. Almost all the analysed items were significantly influenced by the distance between the patient's domicile and the nearest hospital. However, no significant differences were observed comparing the pre-COVID to COVID lockdown.
Table V focuses on the analysis of the patient's comorbidities. No significant differences were depicted.
Table VI summarises gender- and living status-related analysis. No significant differences were observed.

Table I. *Main data of the study.*

	All (n;%)	Female (n;%)	Male (n;%)	p-value
Patients, n (%)	**n=782;100%**	**360;46.04%**	**422;53.96%**	
Age				.061
18-35 years, n (%)	22	12	10	
36-50 years, n (%)	58	36	22	
51-65 years, n (%)	325	145	180	
>65 years, n (%)	377	167	210	
Education				.006*
< High school	72	46	26	
High school	64	30	34	
Degree	646	284	362	
Distance from hospital				.086
<2km	342	152	190	
2-10 km	256	125	131	
10-20 km	39	24	15	
>20 km	145	59	86	
Orthopaedic disease				.454
Trauma	144	63	81	
Osteoporosis	153	68	85	
Osteoarthritis	164	83	81	
Muscle/tendon diseases	156	65	91	
Spine diseases	165	81	84	
Medical comorbidities (i.e., obesity, diabetes, hypertension, dyslipidaemia, ischemic heart disease, COPD, malignancies)				.151
None	542	251	291	
1	206	91	115	
2	17	6	11	
>2	17	12	5	
Living status				.031*
Alone	173	77	96	
With 1 or more roommates	314	142	172	
With wife or husband	111	65	46	
With wife/husband and children	184	76	108	
Physical activity level:				
Level 0: Illness or disability pension	13	9	4	<.001*
Level 1: Sedentary work	199	102	97	
Level 2: Light work or walks on uneven ground but impossible excursions	105	53	52	
Level 3: Light jobs	131	69	62	
Level 4: Moderate heavy work	56	28	28	
Level 5: Heavy work, competitive sport-cycling, cross-country skiing, recreational sport, jogging on uneven ground at least 2 times a week	118	49	69	
Level 6: Recreational sport, tennis and badminton, handball, racquetball, skiing (downhill), jogging at least 5 times a week	96	35	61	
Level 7: Competitive sport-tennis, running, handball, recreational sport, soccer, football, rugby, ice hockey, basketball, squash, racquetball, running	41	10	31	
Level 8: Competitive sport, racquetball, bandy, squash or badminton, athletics, skiing (downhill)	4	0	4	
Level 9: Competitive sport, soccer, football, rugby (lower leagues), ice hockey, wrestling, gymnastics, basketball	15	5	10	
Level 10: National competitive sport, soccer, football, rugby	4	0	4	

Table II. *Gender and age-related analysis*

	Before COVID-19 pandemic									During lockdown									
	Female (n=360; 46%)				Male (n=422; 54%)				p-value*	Female (n=360; 46%)				Male (n=422; 54%)				p value[b]	p value[c]
	18-35 yrs.	36-50 yrs.	51-65 yrs.	>65 yrs.	18-35 yrs.	36-50 yrs.	51-65 yrs.	>65 yrs.		18-35 yrs.	36-50 yrs.	51-65 yrs.	>65 yrs.	18-35 yrs.	36-50 yrs.	51-65 yrs.	>65 yrs.		
Referral to a general practitioner (No/Yes)	4 8	25 11	84 61	94 73	9 13	41 17	183 142	199 178	.692	10 0	27 5	96 38	99 39	8 2	12 10	118 62	113 97	.302	.498
Referral to Orthopaedic surgeon (No/Yes)	7 5	30 6	101 44	106 61	15 7	47 11	217 108	234 143	.634	8 4	26 10	100 45	85 82	15 7	41 17	206 119	188 189	.705	.547
Call the general practitioner (No/Yes)	3 9	29 7	88 57	89 78	6 16	44 14	185 140	196 181	.825	8 4	29 7	88 50	110 49	15 7	36 22	221 104	256 121	.141	.737
Call to Orthopaedic surgeon (No/Yes)	7 5	32 4	103 42	106 61	14 8	49 9	210 115	240 137	.298	7 5	26 10	96 49	96 71	14 8	37 21	212 113	224 153	.175	.430
Referral to Emergency Department (No/Yes)	8 4	32 4	118 27	114 53	16 6	51 7	254 71	257 140	.695	12 0	36 0	142 3	166 1	21 1	55 3	315 3	377 0	.137	.928
Reported compliance in drug assumption (No/Yes)	12 0	30 6	129 16	152 15	20 2	51 7	285 40	337 40	.211	4 8	16 20	74 71	107 60	8 14	22 36	185 140	238 139	.161	.160
Reported compliance in local therapy** (No/Yes)	6 6	10 26	57 88	74 93	8 14	16 42	135 190	174 203	.473	4 8	11 25	50 95	84 83	7 15	19 39	131 194	201 176	.863	.867
Look for info about your health condition on the net (No/Yes)	5 7	21 15	90 55	119 48	9 13	36 22	04 121	274 103	.933	9 3	16 20	81 64	75 92	11 11	24 34	171 154	171 206	.080	.334
Fear of COVID-19 infection (No/Yes)										2 10	12 24	31 114	37 132	5 17	18 40	63 262	79 298	.784	

*a=Multivariate Analysis between Females and Males Before COVID-19 pandemic; b= Multivariate Analysis between Females and Males During lockdown; c= Multivariate Analysis between Females and Males and Before and During COVID-19 pandemic; *=p value<0.05.*

Table III. *Gender and education level*

	Before COVID-19 pandemic							During lockdown							
	Female (n=360; 46%)			Male (n=422; 54%)			p value[a]	Female (n=360; 46%)			Male (n=422; 54%)			p value[b]	p value[c]
	< High school	High school	Degree	< High school	High school	Degree		< High school	High school	Degree	< High school	High school	Degree		
Referral to the general practitioner (No / Yes)	26 20	18 12	163 121	17 9	24 10	184 178	.234	34 14	16 14	182 102	22 4	22 12	207 155	.277	.845
Referral to Orthopaedic surgeon (No / Yes)	36 10	24 6	184 100	25 1	26 8	218 144	.179	40 6	22 8	157 127	23 3	29 5	179 183	.332	.699
Call to the general practitioner (No / Yes)	27 19	22 8	160 124	17 9	26 8	179 183	.451	30 16	21 9	184 100	15 11	15 11	247 115	.051	**.029***
Call to Orthopaedic surgeon (No / Yes)	36 10	26 4	186 98	23 3	27 7	215 147	.395	31 15	22 8	172 112	18 8	24 10	237 125	.536	**.050***
Referral to Emergency Department (No / Yes)	43 3	28 2	201 83	26 0	32 2	248 114	.716	45 1	29 1	282 2	26 0	34 0	348 14	.228	.916
Reported compliance in drug assumption (No / Yes)	38 8	26 4	259 25	19 7	30 4	321 41	.587	22 24	18 12	161 123	13 13	8 26	231 131	**.003***	**.007***
Reported compliance in local therapy (intraarticular injections; shock waves therapy; physiokinesistherapy) (No / Yes)	14 32	9 21	124 160	8 18	10 24	168 194	.954	11 35	3 27	135 149	2 24	5 29	202 160	.139	.457
Look for info about your health condition on the net (No / Yes)	23 23	15 15	197 87	10 16	17 17	261 101	.488	11 35	3 27	135 149	17 9	14 20	165 197	.450	.239
Fear of COVID-19 infection (No / Yes)								17 29	7 23	57 227	8 18	9 25	67 295	.808	

*a=Multivariate Analysis between Females and Males Before COVID-19 pandemic; b= Multivariate Analysis between Females and Males During lockdown; c= Multivariate Analysis between Females and Males and Before and During COVID-19 pandemic; *=p value<0.05.*

Table IV. *Gender and distance from the hospital*

	Before COVID-19 pandemic									During lockdown									
	Female (n=360; 46%)				Male (n=422; 54%)				p value[a]	Female (n=360; 46%)				Male (n=422; 54%)				p value[b]	p value[c]
	<2km	2-10km	10-20km	>20km	<2km	2-10km	10-20km	>20km		<2km	2-10km	10-20km	>20km	<2km	2-10km	10-20km	>20km		
Referral to the general practitioner No / Yes	107 45	61 64	15 9	24 35	130 60	56 75	10 5	29 57	**<.001***	102 33	80 30	15 6	35 13	118 72	81 50	8 7	44 42	.110	.847
Call to the general practitioner No / Yes	106 46	68 57	15 9	20 39	122 68	64 67	9 6	27 59	**<.001***	101 51	75 50	16 8	43 16	122 68	85 46	11 4	59 27	.234	.830
Referral to Orthopaedic surgeon No / Yes	127 25	74 51	19 5	24 35	153 37	70 61	10 5	36 50	**<.001***	125 27	66 59	14 10	14 45	153 37	57 74	4 11	17 69	**<.001***	.924
Call to Orthopaedic surgeon No / Yes	127 25	78 47	19 5	24 35	148 42	69 62	10 5	38 48	**<.001***	95 57	83 42	14 10	33 26	135 55	84 47	11 4	49 37	**.029***	.428
Referral to Emergency Department No / Yes	141 11	87 38	20 4	24 35	177 13	79 52	10 5	40 46	**<.001***	151 1	122 3	24 0	59 0	182 8	125 6	15 0	86 0	.110	.249
Reported compliance in drug assumption No / Yes	130 22	11 7 8	21 8	55 4	158 32	118 13	12 3	82 4	**.003***	58 94	82 43	15 9	46 13	82 108	85 46	13 2	72 14	**<.001***	.529
Reported compliance in local therapy** No / Yes	38 114	62 63	10 14	37 22	53 137	69 62	6 9	58 28	**<.001***	30 122	58 67	11 13	50 9	47 143	78 53	11 4	73 13	**<.001***	.452
Look for info about your health condition on the net No / Yes	74 78	86 39	21 3	54 5	94 96	102 29	13 2	79 7	**<.001***	86 66	70 55	11 13	41 45	103 87	65 66	6 9	22 64	**<.001***	.588
Fear of COVID-19 infection No / Yes										43 109	25 100	9 15	4 55	55 135	16 115	3 12	10 76	.253	

*a=Multivariate Analysis between Females and Males Before COVID-19 pandemic; b= Multivariate Analysis between Females and Males During lockdown; c= Multivariate Analysis between Females and Males and Before and During COVID-19 pandemic; *=p value<0.05.*

Table V. *Gender and medical comorbidities (i.e., obesity, diabetes, hypertension, dyslipidaemia, ischemic heart disease, COPD, malignancies)*

	Before COVID-19 pandemic									During lockdown									
	Female (n=360; 46%)				Male (n=422; 54%)				p value[a]	Female (n=360; 46%)				Male (n=422; 54%)				p value[b]	p value[c]
	None	1	2	>2	None	1	2	>2		None	1	2	>2	None	1	2	>2		
Referral to the general practitioner No / Yes	151 100	49 42	1 5	6 6	160 131	59 56	4 7	2 3	.788	158 93	60 31	5 1	9 3	163 128	79 36	5 6	4 1	.188	.170
Call to the general practitioner No / Yes	157 94	47 44	2 4	3 9	155 136	59 56	5 6	3 2	.244	174 77	52 39	2 4	7 5	191 100	76 39	6 5	4 1	.710	.908
Referral to Orthopaedic surgeon No / Yes	170 81	59 32	4 2	11 1	190 101	67 48	8 3	4 1	.910	152 99	55 36	1 5	11 1	155 136	63 52	8 3	5 0	.088	.165
Call to Orthopaedic surgeon No / Yes	177 74	58 33	4 2	9 3	184 107	70 45	7 4	4 1	.914	153 98	60 31	4 2	8 4	192 99	77 38	7 4	3 2	.894	.632
Referral to Emergency Department No / Yes	189 62	67 24	4 2	12 0	211 80	80 35	10 1	5 0	.677	250 1	89 2	6 0	11 1	282 9	111 4	10 1	5 0	.552	.532
Reported compliance in drug assumption No / Yes	221 30	87 4	5 1	10 2	259 32	99 16	8 3	4 1	.231	134 117	50 117	6 0	11 1	170 121	70 45	8 3	4 1	.560	.522
Reported compliance in local therapy** No / Yes	97 154	43 48	4 2	3 9	124 167	58 57	3 8	1 4	.392	107 144	37 54	4 2	1 11	147 144	57 58	4 7	1 4	.507	.986
Look for info about your health condition on the net No / Yes	164 87	62 29	4 2	5 7	20 88	79 36	5 6	1 4	.525	119 132	50 41	3 3	9 3	132 159	55 60	5 6	4 1	.923	.739
Fear of COVID-19 infection No / Yes										54 197	23 68	1 5	3 9	54 237	28 87	1 10	1 4	.983	

*a=Multivariate Analysis between Females and Males Before COVID-19 pandemic; b= Multivariate Analysis between Females and Males During lockdown; c= Multivariate Analysis between Females and Males and Before and During COVID-19 pandemic; *=p value<0.05.*

DISCUSSION

At the beginning of the second decade of the 21st century, in the era of Medicine 4.0, the healthcare systems worldwide fought the COVID-19 challenge. Italy was the first country to lockdown in Europe to struggle with the new coronavirus diffusion. This choice revealed helpful in flattening the COVID-19 curve but revolutionised several aspects of our lives.

Ruggieri et al. (11) have investigated the impact of gender differences on COVID-19 infection in Italy, depicting a higher mortality rate in male patients (14.8%) compared with female patients (8.2%). These authors suggest that biological (i.e., sexual hormones, X-linked gene expression and differential ACE2 expression levels) and lifestyle differences might explain these gender-related differences.

Moreover, Galasso et al. (12) analysed data from a survey conducted in March and April 2020 in eight Organization for Economic Co-operation and Development countries (n = 21,649) to study gender differences in COVID-19−related beliefs and behaviours. These Authors showed that women are more likely to perceive COVID-19 as a severe health problem, to agree with restraining public policy measures and comply with them.

This study has focused on analysing gender and socio-economic issues in the clinical assessment of Orthopaedic patients during the COVID-19 lockdown, compared with the pre-COVID-19 period. Gender, age, education level, distance from the hospital, number of medical comorbidities and living status were analysed. Gender and education level reveal the most relevant factors influencing the patients' social behaviour during the COVID lockdown, compared to the pre-COVID period. Patients' domicile distance from the nearest hospital also had a relevant impact on the patient's behaviour, but no significant differences were observed during the COVID lockdown compared to the pre-covid period.

Concerning the perceived risk of contracting the COVID-19 infection, Abrams et al. (13) have emphasised the role of risk communication during the COVID pandemic. Therefore, the fear of contracting COVID-19 disease is as real as the physical danger itself. The present study highlighted some aspects of the pandemic that can heighten the risk perception, i.e.; the so-called dread factors, that broadly apply to the current pandemic. These factors include high infection rates, COVID significant morbidity and mortality, the low availability of face masks and personal safety devices, the lack of therapeutic measures and the rapid virus spread.

These factors could underestimate the perception of risk among the general population, and, at the same time, they could also underestimate the importance of compliance with the restriction rules. Our data confirm the findings reported by Abrams et al. (13) since the vast majority (71.22%) of participants, in the absence of gender differences ($p=0.082$), reported a quite high contagion perception risk.

Furthermore, Abrams et al. (13) have also emphasised that daily headlines generate widespread fear and panic; and the World Health Organization (WHO) reported that a significant part of effective communication risk includes identifying and managing rumours and misinformation. In this context, our data support the report by Abrams et al. since 304 women (38.87%) and 264 men (33.76%) affirmed they had a medium-high level of fear of contracting the infection. This finding has probably promoted respect for the limitations imposed by the Italian government: 355 women (45.40%) and 411 men (52.56%) affirmed they paid attention to adopting all the measures needed to reduce the risk of SARS-CoV-2 infection.

Moreover, Jungmann et al. (14) highlighted that health anxiety and cyberchondria had increased SARS-CoV-2 anxiety. Jungmann et al. also observed that anxiety is negatively related to the degree of information about the pandemic status. Our data agree with this finding since the participants' psychological level and perception of their level of information on the pandemic condition are good.

The findings reported in the present study are useful for planning future public health policies to improve patient care and optimise patient compliance.

CONCLUSION

Patients' gender and education level in the present study revealed a significant impact on their social behaviour during the COVID lockdown, compared with the pre-COVID period. In addition, patients' domicile distance from the nearest hospital also plays an important role in influencing patients' behaviour and clinical compliance. These findings are useful to better plan future public health policies.

Conflicts of Interest:

The authors declare no conflict of interest.

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Evaluation Study

TREATING THE MICRO INSTABILITY WITH PERCUTANEOUS CT GUIDED TRANSFACETAL FIXATION: A 15-YEAR EXPERIENCE

L. Manfrè[1], A.E. De Vivo[2], H. M. Alqatani[3], J. Hirsh[4], B. Beomonte Zobel[5], M. Midiri[6] and M. Bonetti[6]

[1]Minimal Invasive Spine Therapy Department, Mediterranean Institute for Oncology, Viagrande, Catania, Italy;
[2]Department of Radiology, Campus BioBiomedicaliversity, Roma, Italy;
[3]Department of Neuroradiology, Hamad General Hospital, Doha, Qatar;
[4]Department of Neuroradiology, General Massachusetts Hospital MAsGEn, Boston, U.S.
[5]Department of Radiology, University of Palermo, Palermo, Italy;
[6]Department of Neuroradiology, Istituto Clinico Città di Brescia, Brescia, Italy

Correspondence to:
Luigi Manfrè, MD
Minimal Invasive Spine Therapy Department,
Mediterranean Institute for Oncology,
Corso Italia 10, 95129 Catania, Italy
e-mail: lmanfre@me.com

ABSTRACT

Axial microinstability secondary to disc degeneration and consequent chronic facet joint syndrome (CFJS) is a well-known pathological entity, usually responsible for low back pain (LBP). Despite posterior lumbar fixation has been widely used for lumbar spine instability and LBP, a complication related to wrong screw introduction, perineural scars, and extensive muscle dissection leading to muscle dysfunction has been described. Radiofrequency ablation of facet joints zygapophyseal nerves conventionally used for pain treatment fails in approximately 21% of patients. We investigated the "covert-surgery" minimally invasive technique in treating local spinal instability and LBP, using a novel fully-CT-guided approach in patients affected by axial instability and complicated by CFJS resistant to radio ablation. We introduced fully- or partially-treated trans-facet screws directly to achieve solid arthrodesis, reducing instability and LBP, thus a retrospective study was performed. All patients in simple analogue sedation perfectly tolerated the CT-guided procedure, and the mean operative time was approximately 45 minutes only. All 67 patients treated underwent clinical and CT study follow-up at 2 months, revealing LBP disappearance in 50 patients and a significant reduction of lumbar pain in 17 patients. In conclusion, CT-guided trans-facet screws is a fast and safe technique when posterior facet fixation is needed.

KEYWORDS: *spine, instability, fixation, CT*

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INTRODUCTION

Many factors, including axial micro-instability secondary to disc herniation, can cause low back pain (LBP). Among the causes of the so-called chronic facet joint syndrome (CFJS) are asymmetrical load at the level of local facet joints, abnormal degeneration of the articular cartilage and bone remodelling of the joints (1). In turn, CFJS is regarded as one of the most common causes of LBP in patients of older age and even in younger people.

Posterior lumbar fixation (PIF) has been adopted as one of the most recurring therapies for lumbar spine instability and LBP. This method uses transpedicular screws and posterior fixating rods to reduce the abnormal movement of a segmental functional spine unit (FSU). However, in literature, complications linked to PIF are documented, such as perineural scars and extensive muscle dissection, up to the point of muscle dysfunction (1).

The correct placement of pedicle screws on the very first try is required to obtain maximum stability. However, complications related to incorrect position of screws with neurologic o vascular damage have also been reported (2-8). Finally, possible complications related to general anaesthesia should be taken into account.

Another therapy used in pain treatment related to CFJS (9) is radiofrequency ablation (RFA) of facet joint zygapophyseal nerves. However, a significant percentage of treatment failure is reported, with persistent LBP even in patients undergoing more than one treatment.

In this study, we intended to investigate a "covert-surgery" minimally invasive technique in treating local spinal instability and LBP, using a novel fully-CT-guided approach in a patient affected by FSU axial instability complicated by CFJS resistant to radio ablation by introducing direct fully or partially treated trans-facet screws (trans-facet fixation - TFF), to acquire solid arthrodesis, reducing instability and LBP.

MATERIALS AND METHODS

From March 2006 to November 2021, we treated 304 patients affected by LBP related to CFJS. Referred pain was assumed to be 10 (maximum) before the treatment, compared to clinical results after the treatment. All the patients underwent conventional axial CT (General Electric, Milwaukee, MA) study of the disc space between L3 and S1 level and a lumbar MRI (1.5T, Intera, Philips – Erlangen) study including axial and sagittal T2-STIR images, and contrast-enhanced T1SE scan with fat-saturation technique, demonstrating indirect signs of local instability (i.e. black disc, facet joints deformation and/or sclerosis, peri-articular inflammatory reaction, pedicle oedema or degenerative synovial cysts). To confirm the articular origin of LBP, we performed a CT-guided introduction of 1cc of lidocaine at the level of the zygapophyseal nerve of the presumed facets responsible for LBP. In addition, all the patients underwent CT-guided zygapophyseal nerve radio ablation (pulsed radio ablation, 90 degrees for 180 seconds), and clinic follow-up at 2 months was performed. Although most of the population referred significant (more than 70%) reduction of LBP 60 days after RFA treatment, a pool of patients complained about a poor decrease in lumbar pain (less than 20% than the original), and for this reason, a second RFA procedure was performed. However, despite the second treatment, no LBP reduction was appreciated. After being informed about it, the remaining 67 patients were accepted to undergo CT-guided trans-facets fusion (TFF) of zygapophyseal joints at the presumed pain level (25 cases at L4/L5 level, 42 cases at L5/S1).

TFF was obtained using a "one-step" fully percutaneous procedure (ILLICO FS ® – Alphatec Spine, Carlsbad, CA). For the patient lying prone on the CT table, a C-arm was positioned for lateral view, and a low-dose (10mA/120kV) 2.5mm study was obtained. First, a 5cc lidocaine injection using a 20G spinal needle was performed to obtain local anaesthesia into deep muscular tissue and peri-articular area. After that, the 11G Jamshidi needle was introduced on an oblique orientation, the entry point being approximately at the level of the spinous process two levels above the selected joints, driving the needle to the inferior articulating process of the level above. The needle tip was then introduced through the articular rim over 10 to 15mm and into the superior process at the level below. Then, the inner stylet was removed, and a guidewire through the targeting needle was placed. After removing the Jamshidi cannula, firmly maintaining the guidewire into the selected place, surrounding soft tissues and muscles were dilated using coaxial dilators with a small 10mm skin incision. A manual driller was placed over the guidewire and advanced across the facet joint and into the pedicle. In-vivo measurement of the distance between the cortex of the inferior process of the level above and the pedicle

of the level below was performed using CT scans and partially treated trans-facet surgical-grade titanium alloy screws were selected (35mm length in 50 patients, 45mm length in 17 patients). Using a screwdriver, screws were introduced along the guidewire, perfectly centred to the articular process bilaterally (Fig. 1-2-3-4). Finally, the guidewire and the dilator were removed, and the skin was sewn. Post-op CT control was always performed immediately after the procedure and 60 days after as a follow-up control. Only mild analogue sedation (Fentanil 1 to 3gamma/kg/h / Remifentanil 0.2 to 0.3gamma/kg/h) was performed during the procedure.

After 2 months, all patients underwent MRI scan follow-up (Fig. 5).

RESULTS

All patients perfectly tolerated the CT-guided procedure in simple analogue sedation, and the mean operative time was approximately 45 minutes only. All 67 patients treated underwent clinical and CT study follow-up at 2 months, revealing

Fig 1. *L5-S1 microinstability. Sagittal 2D reformatted scan: the delivery system with a 6mm diameter muscle dilator allows the correct positioning of L5-S1 transfaccettal screw.*

Fig 2. *Coronal scan at the level of L5-S1. The screw crowns are symmetrically oriented.*

Fig 3. *Post-op axial 2D recon at L5-S1 level. To obtain the maximal fixation effect, screws must be symmetrical and divergent.*

LBP disappearance in 50/67 patients and a significant reduction of lumbar pain in 17/67 patients.

In 25/67 patients, a follow-up CT study demonstrated the correct position of bilateral trans-facet screws with a fusion of the facet joints at the L4/L5 and L5/S1 levels in 42/67 patients. No significant para-spinal and/or muscular scar was appreciated on CT scans. In addition, none of the patients reported a remarkable reduction of flexion/extension movement, and no other side effect was noted.

Pain resolution occurred in the patient affected by severe right L5/S1 joint degeneration with synovial cysts, pedicle oedema and bone sclerotic reaction, despite the partial introduction of the right TFF related to unilateral pedicle bone sclerosis. This effect was probably related to the joint block obtained thanks to the contralateral screw.

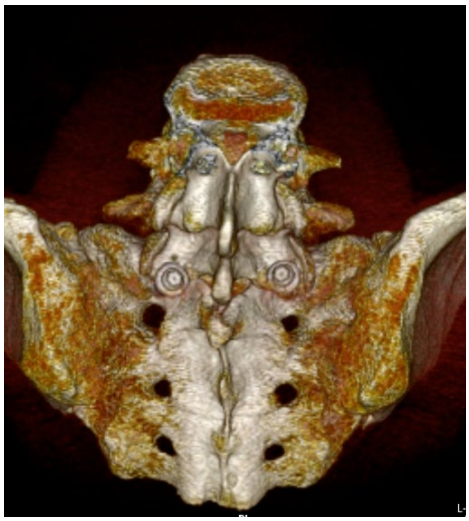

Fig 4. *L5-S1 transfaccettal fixation 3D recon. The external crown and screws are clearly depicted above the inferior L5 facet surface.*

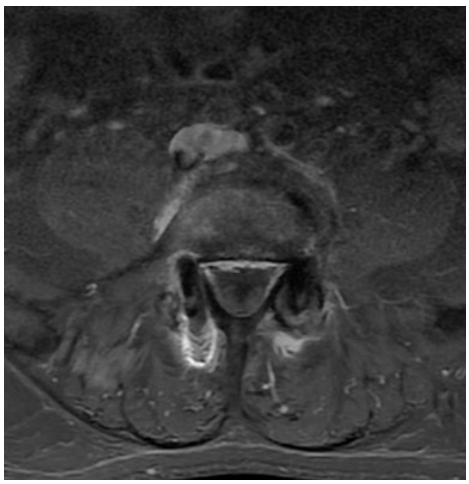

Fig 5. *Axial contrast enhanced MRI follow-up at 2 months: the MRI clearly shows normal bone signal around the screws, that are hypo intense according to the titanium structure.*

DISCUSSION

Among the causes of chronic lumbar pain in young and elderly patients, facet joint disease, generally related to chronic arthritis and/or segmental degeneration, remains among the most common. Despite the wide use of radiofrequency ablation of the zygapophyseal nerve for pain control in patients affected by CFJS, treatment failure occurs in approximately 21% of patients, probably because of incomplete nerve radio ablation determined by wide anatomical variability (10). In addition, this failure percentage significantly increases in patients who previously underwent laminectomy (59% of failure) or PIF (71%) (11-12). For this reason, a more aggressive approach should be considered in case of RFA failure and persistent LBP related to spinal instability.

Conventional PIF is generally used in painful lumbar spinal instability to lock the vertebras, reducing the LBP related to excessive movement. However, in the literature several drawbacks of this procedure have been pointed out, generally related to incorrect screw positioning. In addition, excessive rigidity of the spinal implant can increase stress transmitted to contiguous FSU, with accelerated disc degeneration/herniation, as well as generating painful subchondral bone oedema related to stress shearing impact (13-14).

The lateral interbody fusion (LIF) technique for lumbar interbody arthrodesis has been recently proposed, with good biomechanical stability of stand-alone cage placement compared to posterior fixation obtained with the PIF technique (15). However, LIF surgical approach remains as "aggressive" as PIF one, and general anaesthesia is always needed. Moreover, both therapy techniques include extensive deep paraspinal muscles dissection, leading to muscle dysfunction and increasing general instability of the spine.

Trans-facet pedicle screw fixation provides similar acute stability to the lumbar spinal segment compared to traditional lateral interbody cage fixation (Fig. 6) or posterior interbody fusion (16), and even cervical application has been recently proposed (17-18).

TFF has been shown to provide near biomechanical equivalence to LIF and PIF. Because no general anaesthesia is required and its total working time is inferior to one hour, this therapy significantly reduces operative time and morbidity (19). Trans-facet screws demonstrated statistically similar stiffness to cyclic flexion/extension, lateral bending, and torsion of the lumbar spine compared to conventional PIF. The anterior column loading during several physiologic tests showed no biomechanical differences between TFF and PIF stabilization. Moreover, TFF reduces soft tissue disruption

preserving the adjacent facet joint (20), respecting muscle anatomy as deep dissection is not necessary with a fully percutaneous approach.

Fully CT-guided TFF has not been described yet in the literature. Using a real-time 2D CT study performed during the procedure, it was easy to calculate optimal screw length, thickness and desired orientation, reducing the risk of complications related to improper screw insertion and avoiding the need to retrieve and re-introduce screws in case of initial incorrect positioning; an action that is responsible for increasing screw instability related to bone erosion (21). Consequently, as screws must be placed in the correct position on the very first try, CT guided approach is a useful and powerful technique, for it reduces the failure of surgical stabilization.

In all the patients treated but one, introducing the screws was an easy one-step procedure, performed in approximately 15 min on each side, and no pain was referred, thanks to mild analogue/sedation. In the patient affected by L5/S1 microinstability with severe right S1 pedicle bone sclerosis, the introduction of the right screw was not completed because of difficulty in drilling the severely sclerotic pedicle. However, the screw overpassed the articular rim and LBP resolution after stabilization was achieved, thanks to the fully introduced contralateral screw on the other side.

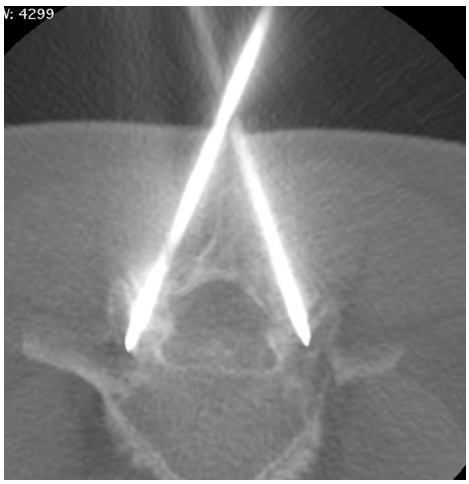

Fig. 6. *L5-S1 transfaccettal fixation: first step. Two 13G trocars are introduced passing through the inferior facet of L5 and the superior S1 one, to prepare the coaxial introduction of the guide wire and screws.*

Although trans-facet fixation can be performed at L3-S1 level by using the simple C-arm and the "inferior endplate and medial pedicle wall of the superiorly instrumented level as anatomic landmarks in conjunction with axial and sagittal angles of insertion" (22-23), CT guided technique provides additional advantages to conventional radioscopic approach. In the case of the facet joint and pedicle deformation related to long-standing axial instability, X-ray lateral and antero-posterior views can be unsafe because of the difficult visualization of conventional landmarks. On the contrary, the CT-guided approach (thanks to a real-time evaluation of the patient anatomy) allows the ad-hoc orientation of the Jamshidi needle and guidewire to be adopted, evaluating the foramina and nerves, as well as vascular structures nearby (Fig. 4). Moreover, the correct length and thickness size of the screws can be explicitly chosen in each case, for every patient, measuring the pedicle diameter and length on 2D CT recons, avoiding incorrect choice of screw size too much short, long or thick.

All patients tolerated well analgo-sedation using opioids: besides reducing eventual complications related to general anaesthesia, the technique allowed to reduce significantly the total working time (approximately 45 minutes only), which is half the time generally needed for a conventional surgical TFF, even on a lateral approach, as described in the recent literature (24-26).

CONCLUSION

It appears that TFF can be a powerful technique in the case of lumbar spine stabilization in patients suffering from CFJS, and no side effects or complication was observed. Mean working time was significantly reduced using a fully CT-guided technique in simple analgo-sedation. In conclusion, CT-guided TFF is a fast and safe technique when posterior facet fixation is needed.

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Letter to the Editor

DENTAL ABSCESSES AND PHLEGMONS: A BRIEF REVIEW

M. Petruzzi[1], S. Messina[1], D. De Falco[2], A. Lucchese[3], A. Romano[3], D. Di Stasio[3], L. Milillo[2] and M. De Benedittis[2]

[1]Section of Dentistry, Department of Interdisciplinary Medicine, University of Bari "Aldo Moro", Bari, Italy;
[2]Private Practice, Bari, Italy;
[3]Multidisciplinary Department of Medical and Dental Specialties, University Vanvitelli, Naples, Italy

Correspondence to:
Massimo Petruzzi, DDS,
Section of Dentistry, Department of Interdisciplinary Medicine, University of Bari "Aldo Moro",
Piazza Giulio Cesare 11, 70125 Bari, Italy
e-mail: massimo.petruzzi@uniba.it

ABSTRACT

One of the most frequent dental emergencies is represented by abscesses and odontogenic phlegmons. The acute onset can cause trismus, pain, fever, and, in severe cases, impaired patient breathing. The colliquation of the phlegmonous or abscess collection and their drainage, together with adequate antibiotic therapy, remain the fundamental prerequisite to avoiding severe complications and restoring masticatory function.

KEYWORDS: *dental abscess, dental phlegmon, oral infections, fever, trismus*

INTRODUCTION

The term "dental abscess" is referred to a well-circumscribed puss collection caused by dental-related infections. Usually, the puss collection is located in the deep and superficial neck spaces. On the other hand, phlegmon is a non-circumscribed suppurative process with an expansive and diffusive tendency (1).

Dental abscesses and phlegmons recognize the same causes, namely pulp infection consequential to caries or traumatic and physical necrosis, residual necrotic roots, periodontal infections, dysodontiasis of the third molar, secondary infections of cysts or dental granulomas (2). Abscess and phlegmons in the oro-maxillofacial area can also recognize non- odontogenic causes such as salivary gland infections, sequelae of radio-chemo-induced osteomyelitis, or (more rarely) the presence of foreign bodies in the oral tissues (3).

Pyogenic bacteria such as beta-haemolytic streptococci*, S. pyogenes*, and anaerobic bacteria typical of the oral microbiota such as *Bacteroides spp*., *Fusobacterium necrophorum and nucleatum, Prevotella melaninogenica and Porphyromonas spp*. represent the most involved bacteria in the abscess and phlegmons genesis. The presence of an abscess collection with the isolation of *Actinomyces spp* is to be included in the context of oral actinomycosis (4).

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Pathogenesis

In the most classic case series, the infectious process recognizes a departure from the necrotic pulp of a tooth. A strong bacterial load and/or an ineffective immune response on the part of the host can cause the spread of infections to the periapical tissues, alveolar bone, and soft tissues. The puss that accumulates during the abscessualization process tends to collect in newly formed intra-tissue cavities (abscess) or can spread through the muscle bands and mucous layers, leading to the establishment of a phlegmon. The puss tends to drain through the *loci minoris resistentiae*, making its way between the oral and extraoral tissues, forming one or more fistulous tracts (5). Bacterial products digest the affected tissues, and intense inflammation occurs in the abscess / phlegmonous area (peri ascessual cellulite). Abscess drainage can spontaneously occur in the oral cavity, in maxillary sinuses, or drain into the peri and parapharyngeal spaces, up to the mediastinum, with life-threatening complications if not promptly treated (6).

The formation of abscesses can also occur due to the exacerbation of periapical granulomas, superinfection of included or semi-included dental elements, cysts, and teeth with deficient endodontic or conservative treatments (7).

Clinical aspects

The abscess or phlegmons formation can be preceded by odontalgia or begin without unusual dental symptoms. In its florid phase, the abscess presents as a swelling localized to the face in the genial region, submandibular, on the oral floor. It spreads to the periorbital regions (canine abscesses and upper premolars). The overlying skin may be red and hot. Palpation generates pain, and if the abscess is already colliquated, an inevitable fluctuation of the purulent contents can be appreciated. The hard-wood consistency will indicate an absent or incomplete colliquation of the abscess / phlegmonous content (8).

Trismus (inability to open the mouth), fever, malaise, and headache can be associated. In addition, the patient may complain of dysphagia or dyspnea, symptoms indicative of pharyngeal involvement and the urgency of treatment (9).

Diagnosis

First and possibly second-level radiological investigations clinically support the diagnosis. The oral examination will identify the causative dental element, and the orthopantomographic examination will confirm the presence of any odontogenic causes of an abscess. In case of compromise of the airways, maxillary sinuses, or in doubtful cases, it is advisable to perform a CT scan that highlights the patency of the air spaces and makes it easier to appreciate the extent of the infectious process affecting the oro-maxillofacial tissues. The collection of purulent material is useful for microbiological diagnosis and possible antibiogram (1-3).

Treatment of dental abscesses

Treatment is primarily medical. Adequate antibiotic therapy must be established with the extent of the abscess and the patient's compliance. Amoxicillin associated with clavulanic acid according to weight and age is the first-choice therapy, especially in the case of small abscesses without the involvement of the perioral or extraoral tissues. An NSAID is associated with antibiotics for managing inflammation and pain (10).

In more voluminous abscesses or refractory to oral therapy, intramuscular therapy with penicillin or cephalosporins is necessary, while in more complex cases with the risk of compromising the airways or septicemia, it is advisable to hospitalize the patient. Treatment of hospitalized patients involves using polyantibiotic therapies with penicillin, metronidazole, imipenem, or teicoplanin, also based on the response of the antibiogram.

Surgical treatment involves drainage of the abscess collection after intraoral and/or extraoral incisions. The incision occurs after the abscess collection colliquation has been ascertained. Subject to surface anaesthesia, the abscess synechiae are incised and debrided to allow the puss to escape. Finally, gauze or a drainage tube is applied, which will be replaced in the following days.

Surgical treatment could also include the avulsion of the causal dental element (e.g., third molar or necrotic roots) with trans-alveolar drainage of the puss (11).

In other cases, however, the devitalization of the necrotic dental element causing the abscess is necessary. The drainage will occur through the root canal or canals, which will be cleaned with irrigating solutions based on sodium hypochlorite and filled with dedicated materials (12).

Complications of odontogenic abscesses

Sepsis or septicemia is one of the most feared complications of odontogenic abscesses and phlegmons. The bacterial load can spread by hematogenous route, especially in cases of particular immunodepression of the patient (13). Osteitis and osteomyelitis can occur due to the involvement of the bone tissue by the infectious process (14).

Ludwig's angina is a complication with a potentially poor prognosis if not adequately recognized and treated. It is characterized by the spread of the abscess and/or phlegmonous process to the neck and oral floor's lodges and anterior fascial spaces. Sialorrhea, trismus, dysphagia, and stridor caused by laryngeal oedema and lifting of the back of the tongue against the palate may be present. The condition can cause airway obstruction in a short time. In addition, the infectious process can continue into the mediastinum and cause mediastinitis (15).

The spread of the infectious process could affect the maxillary sinuses (full) or, in the most severe cases, also cause brain abscesses (16).

CONCLUSIONS

One of the most frequent dental emergencies is represented by abscesses and odontogenic phlegmons. Drainage, together with adequate antibiotic therapy, remain the fundamental prerequisite to avoiding severe complications and restoring masticatory function.

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Letter to Editor

OLLIER'S DISEASE

V. Sollazzo

[1]Medical Director, Medical Centre, Ferrara, Italy

Correspondence to:
Vincenzo Sollazzo MD,
Orthopedic Surgeon, Medical Director, Medical Center, Ferrara, Italy
e-mail: slv@unife.it

ABSTRACT

Spranger type 1 is a rare bone condition known as Ollier's disease (OD). It is characterized by numerous enchondromatosis with a distinctive asymmetrical arrangement. This illness affects only the appendicular bones. There is a lack of complete comprehension of the pathophysiology of enchondromatosis. Several publications have recently proposed that heterozygous mutations in the PTHR1, IDH1, and IDH2 genes can cause OD. Phalanges and metacarpals are the bone structures most frequently affected by multiple enchondromas. OD is characterized by asymmetrical osteolytic lesions that have well-defined sclerotic edges when viewed through the lens of radiology. Even though the therapy is conservative in the vast majority of cases, numerous potential treatment alternatives for challenging patients are explored.

KEYWORDS: *Ollier's disease, enchondromatosis, hyaline, cartilage, bone*

INTRODUCTION

Chondromas are benign tumors most typically found in the hand's phalanges. Chondromas are composed of hyaline cartilage and are almost always asymptomatic. These growths are referred to as enchondromas when they originate in the medullary canal. Chondromas can occasionally develop on the bone surface, termed periosteal and juxtacortical chondromas. Osteochondromas are the most prevalent type of benign cartilaginous tumor. At the same time, enchondromas, second to Ollier's disease (OD), also known as enchondromatosis, is characterized by an abnormal accumulation of cartilaginous ulcerations that can be highly variable in terms of size, multitude, location, transformation, early onset, prognosis, and need for surgery (1). Enchondromatosis is characterized by multiple enchondromas (three or more). The lymphangiomas have been linked to OD and Maffucci syndrome, which is also an enchondromatosis (2, 3). OD is an extremely uncommon form of bone disease that affects just the appendicular skeleton and typically results in an uneven distribution of affected bones. Although it is considered a benign bone tumor, there is a five to fifty percent chance that it will develop into malignant chondrosarcoma. For diagnostic testing, radiographic, histopathological, and morphological examinations are all necessary steps. It is possible to improve the prognosis and minimize tumorigenesis and deformity by gaining a better knowledge of the clinical features and pathological aspects, particularly in patients who are adolescents (4).

The incidence of OD is believed to be one in every 100,000 people (5). Because moderate phenotypes of OD that do not

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involve skeletal deformities are occasionally missed, the true incidence of the disease may be higher than previously thought. Spranger et al. (6) developed a comprehensive categorization of enchondromatosis based on the radiographic appearance, anatomic site, and disease inheritance method. Based on the case descriptions of enchondromatosis, Halal and Azouz (7) later added three subgroups to their categorization system: generalized enchondromatosis with irregular vertebral lesions; generalized enchondromatosis with mucopolysaccharidosis; enchondromatosis with inverted vertebral bodies.

Pathophysiology

There is still much mystery around the process of how enchondromatosis develops. In its most fundamental form, OD is an aberration in the development of the limb bud. When it manifests itself in post fetal life, this error causes the long bones to expand in diameter rather than in length. The idea that enchondromatous lesions are essentially the displaced cartilaginous remains of normal epiphyseal cartilage cells was first postulated by Jaffe and Lichtenstein in 1943. Regarding the origin of enchondroma, this view is still generally recognized as accurate. Anomalies in the signaling pathways that control the proliferation and differentiation of chondrocytes could be to blame for the creation of intraosseous cartilaginous foci in enchondromas. These foci can be found in the bone (8). In patients with OD, the development of enchondromatous lesions can be caused by homozygote mutations and point mutations in the parathyroid-related peptide type 1 receptor (PTHR1) (9). OD has been recently linked to heterozygous mutations in the isocitrate dehydrogenase (IDH) gene, primarily in IDH1 (98%) and IDH2 (2%). These mutations displayed a condition known as antineoplastic mosaicism, similar to that observed in fibrous dysplasia and osteochondroma. The genetic inheritance pattern for OD is unknown, but it is hypothesized that it is not a straightforward Mendelian pattern (10, 11). Because of this, it would appear that OD is the clinical manifestation of a heterogeneous collection of different molecular abnormalities (12).

Clinical features

The following characteristics serve as pathognomonic indicators of OD: beginning in infancy or childhood; radiological changes that are confined to the longitudinal ends of the skeleton with stripped of rarefied areas and subsequent involvement of the epiphysis and the emergence of slight discoloration in the metaphysis and epiphysis in conjunction with the appearance of growth; the existence of cartilage on histological examination in a sample of tissue obtained from the radiolucent region seen on the radiographs. There is significant clinical diversity in the manifestation of OD, particularly concerning the size, quantity, location, and age at which symptoms first appear (13). The symptoms of OD typically appear in the first decade of a person's life. However, the condition has also been observed in adolescents and adults.

These lesions manifest themselves and expand before puberty but quickly transform into normal bone (14). OD affects males twice as frequently as it does females, in contrast to enchondromas, which are equally common in both sexes. Patients typically appear with asymptomatic bone tumors when they are seen. Even though lesions often occur on both sides of the body, with a unilateral preference that results in asymmetric distribution, a symmetric bilateral presentation on both sides has also been recorded (15). Although the appendicular skeleton is the most common site of involvement, the vertebrae of the trunk can also be affected in more severe cases. Enchondromas are uncommon in the carpal bones, as opposed to the phalanges and metacarpals, where they are more typically found. The femur and the tibia are two of the long bones that are commonly affected by OD. The femoral trochanters are typically affected, although the femoral neck is usually spared from the effects of the condition (16). OD can be found in the femoral neck, and it can cause a posterior inclination of the femoral neck fractures epiphysis, which can look like a slipping capital femoral epiphysis. Other bones implicated include pelvis, fibula, and humerus; however, ribs, thorax, and skull are involved only very infrequently; typically, vertebral bones and bones of the craniofacial region are not involved (13). Scoliosis can develop in the pelvis more often than any other trunk bone. The existence of growths on the extremity is the cause of the most prevalent symptom that patients report, which is a cosmetic deformity.

In very unusual cases, bone shortening is the only clinical sign observed. This shortening could result from a problem with the bones' capacity to expand longitudinally. These growth abnormalities are either caused by an abnormal epiphyseal plate adjacent to the enchondromas or by the attachment of the epiphyseal cartilage by an anomalously thick periosteal sleeve formed as a reaction to the enchondromatous lesions. Both of these factors contribute to the condition. It is possible to have an asymmetrical premature physeal arrest, which can result in deformities around the joints. An angular deformity may develop due to the non-uniform distribution of enchondromas, which mainly affect the metaphysis. The concavity of the angular malformation is where vast enchondromatous are located. As the bone expands in a transverse direction, the metaphysis begins to widen and broaden due to this growth (17).

Consequently, abnormalities such as genu valgus and cubitus varus, restrictions in joint motion, and differences in leg length may develop. The weakening of the cortical bone over increasing lesions can lead to pathological fractures. Asymmetry of the face and palsies of the cranial nerves are additional possible complications. OD is characterized by a significantly lower incidence of neural compression than multiple hereditary exostoses (18).

Pathology

A macroscopic evaluation of an enchondroma will typically reveal multiple rounds or oval cartilaginous nodules. These nodules will be limited at their periphery by lamellar bone, and they will be separated from one another by intertrabecular blood and bone spaces in the solid cartilaginous matrix. Myxoid changes will appear as frayed edges of the matrix. On a microscope, there are delineated lobules of mature, hypocellular hyaline cartilage with few double-nucleated cells and slight cytologic atypia. The cellularity of the tumor, on the other hand, may change due to increased mitosis. Islands of developed, nonvesiculated hyaline cartilage cells of varying sizes and shapes are embedded in abnormally rich metachromatic staining extracellular substances inside a network of trabecular bone. There is no indication of any myxoid alteration in the matrix. The processes of calcification and ossification are quite widespread, particularly on the lobules of the cartilage's periphery. This pattern is known as bone encasement (19).

The use of needle cytology is an important part of the diagnostic process for OD. Papanicolaou staining of smears revealed a large number of cartilaginous particles with angular edges. There are also a few spherical dispersed cells and occasionally clustered together. The nuclei of the cells are spherical and arranged in an irregular pattern, and the cytoplasm is plentiful and pale. Binucleation, mild atypia, hypercellularity, and large pleomorphic nuclei are all acceptable markers for benign enchondromas in multiple enchondromatosis (20). These characteristics signal malignancy in a solitary cartilaginous tumor and are present in various enchondromas. Enchondromas and grade I chondrosarcomas are difficult to distinguish from one another until grade I chondrosarcoma demonstrate the distinctive penetration of the bone marrow along with the entrapment of the host's lamellar bone on both sides (20, 21).

It is important to distinguish OD from multiple inherited exostosis. In multiple hereditary exostoses, the localization of bone lesions is the most important factor in distinguishing enchondromas from osteochondromas; this is because osteochondromas are located at the bone surface, whereas enchondromas are located in the center of bones, which enables radiographic distinction between the two (22).

Treatment

OD is typically managed with a conservative approach, except when complications arise. Since the lesions do not cause significant damage to function, they do not need to be addressed. Surgery may be recommended when a patient has a deformity, a limb-length discrepancy, a pathological fracture, or has undergone malignant transformation. The following are some of the primary objectives of the treatment: obtaining the desired level of mechanical alignment; achieving standard walking length to achieve comparable limb length; alleviating the discomfort caused by a pathological fracture. Treatment focuses on the limb affected the most profoundly, as well as any associated abnormalities and consequences (23). Surgery is indicated for an angular deformity that is higher than 25 degrees. Not many therapy options are available for OD, particularly those that can improve the patient's looks (17). Intralesional curettage, which may or may not be accompanied by bone grafting and/or an artificial bone substitute, along with a variety of osteotomies and internal fixations, is a modality that is utilized frequently. These interventions do not address the issue of the uneven distribution of limb length in any way. Curettage and cementing had favorable outcomes in patients with OD affecting the distal femur (24). Osteotomy is possible, but it must be performed multiple times before success. Additionally, the existence of brittle bones is a concern that makes it difficult to do an internal fixation (24).

CONCLUSION

OD is an extremely uncommon condition characterized by asymmetrical and bilateral bone lesions that do not cause pain. The condition manifests as an aesthetic deformity, a limb-length disparity, and pathologic fractures. It is also linked to malignancies, particularly chondrosarcomas, and can cause pathological fractures. The OD must be distinguished from other conditions that can cause bone swellings. OD is often treated with a conservative approach, but reconstructive surgery following an amputation or excision in more severe cases may be necessary. The outlook for someone with OD is generally positive; nonetheless, annual surveillance is recommended for children and adults with the condition.

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Letter to the Editor

PERIODONTAL EHLERS-DANLOS SYNDROME: AN EMERGING GENODERMATOSIS AFFECTING THE ORAL CAVITY

D. De Falco[1*], S. Messina[2] and M. Scivetti[1]

[1]Private Practice, 70126 Bari, Italy; [2]Interdisciplinary Department of Medicine, University of Bari, Bari, Italy;

**Correspondence to:*
Domenico De Falco, DDS
Private Practice, 70126 Bari
e-mail: defalcodomenico@gmail.com

ABSTRACT

Ehlers-Danlos syndrome is an autosomal dominantly inherited genodermatosis. This syndrome has several subtypes, including a periodontal form of Ehlers-Danlos Syndrome (pEDS). The clinical manifestations of pEDS can affect various districts and systems of the body, but oral manifestations are the most frequently encounteredis d. Periodontal lesions are very severe, and young patients tend to lose their teeth early.

Therefore, it is essential to get an early diagnosis. The diagnostic framework is, in fact, fundamental for initiating the management of these patients for the therapeutic plan.

KEYWORDS: c*onnective, laxity, collagen, fibroblast, periodontitis*

Definition and Epidemiology

Ehlers-Danlos syndrome (EDS) is an inherited connective tissue disorder typically characterized by joint hypermobility, skin hyperextensibility, and tissue fragility (1, 2). The current classification of EDS detects 13 subtypes and approximately 19 genes involved in collagen metabolism. A periodontal form is found among the different subtypes of EDS. The periodontal form of Ehlers-Danlos syndrome (EDS VIII) was first described by McKusick in 1972 and classified as a subtype of EDS in 1977 by Steward. (1, 3).

Although it has long been considered a rare syndrome, a recent study published in the BMJ highlighted that EDS has a prevalence of around 20 cases per 10,000 people (4).

Etiology

Periodontal EDS is caused by autosomal pathogenic variants dominant in the C1R (type 1, MIM 613785) and C1S (type 2, MIM 120580) genes, which encode the C1r and C1s subunits of the first component of the classical complement pathway, which has a key role in the innate immune response (5, 6).

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Pathogenesis

Periodontal Ehlers-Danlos syndrome represents the only variant of EDS whose pathogenetic mechanism is closely associated with the innate immune system. The activation of the serine proteases C1s and C1r leads to the activation of the complement cascade at the local level (7, 8).

Clinical findings

Severe periodontitis with early onset is the predominant and characteristic feature of pEDS. The mean age of onset of periodontitis is 14 years (range 2-35 years), with rapid progression. Another distinctive aspect of pEDS is the absence or reduced quantity of adherent gingiva, which causes fragility of the oral tissue and predisposes it to gingival recessions. These clinical features lead these young patients to premature tooth loss (3, 5, 8, 9).

Several general clinical manifestations are described in the literature: almost all individuals with pEDS report easy bruising, especially in the pretibial and atypical areas such as cheeks and thighs. Brownish pretibial plaques may be present following a primary trauma that has not resolved; this reflects significant skin fragility with atrophic scarring and delayed healing. Joint hypermobility often affects only the distal joints. Aneurysms and arterial dissections are also findings described in the literature (8-10).

Diagnosis

Major criteria:
- Severe and intractable periodontitis of early onset (childhood or adolescence)
- Lack of attached gingiva
- Pretibial plaques
- Family history of a first-degree relative who meets clinical criteria

Minor criteria:
- Easy bruising
- Joint hypermobility, mainly distal joints
- Skin hyperextensibility and fragility, abnormal scarring (wide or atrophic)
- Increased rate of infections
- Hernias
- Marfanoid facial features
- Acrogeria
- Prominent vasculature (11)

Minimal criteria suggestive for pEDS:
-Major criterion 1): severe and intractable periodontitis of early onset (childhood or adolescence)
-OR major criterion 2): lack of attached gingiva
-Plus At least two other major criteria and one minor criterion
Confirmatory molecular testing is obligatory to reach a final diagnosis (9).

Treatment

The treatment of odontostomatological manifestations requires certain timeliness due to the severity and rapid onset of periodontitis. Therefore, constant dental visits and periodontal evaluations will be crucial. These patients must be instructed in meticulous oral hygiene with the aid of interdental cleaning devices and brushes (8).

The implant treatment resulting from the loss of teeth does not seem to lead to great results, with very high rates of peri-implantitis and, consequently, implant failure (12).

For this reason, the main goal in managing these patients is to be able to keep their teeth as long as possible (8).

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