Al Direttore Generale
della Fondazione I.R.C.C.S. Policlinico "San Matteo"
Viale Camillo Golgi, 19
27100 Pavia

Il/La sottoscritto/a LISI CLAUDIO chiede di essere ammesso/a a:

**Avviso di pubblica selezione, per titoli e colloquio, per l'attribuzione dell'incarico quinquennale di direzione della Struttura Complessa "SC RIABILITAZIONE SPECIALISTICA" - disciplina di Medicina fisica e Riabilitazione (2022-1.4.2/227) (ID 54886)**

a tal fine dichiara:

**Anagrafica**
Cognome e nome: LISI CLAUDIO
Nato il: [redacted]
Codice Fiscale:

*Documento di riconoscimento*
Tipo di documento: [redacted]
Rilasciato il:

*Indirizzo di residenza*
Residenza: [redacted]
Località:

*Contatti*
Telefono: [redacted]
Mail:

**Requisiti generici**

Cittadinanza: Italia

Comune di iscrizione nelle liste elettorali: [redacted]

Condanne penali riportate: no

Procedimenti penali in corso: no

Posizione rispetto gli obblighi di leva: esonerato

Destituito/dispensato/licenziato dalla P.A.: no

Data pagamento contributo: 03/03/2023

Necessità ausili / Tempi aggiuntivi per l'espletamento del colloquio: No

**Requisiti specifici**

Laurea: Medicina e chirurgia

Università (completa di indirizzo/pec) presso cui ha conseguito la laurea: Università degli Studi di Pavia Indirizzo: Corso Strada Nuova 65, 27100 Pavia; PEC : amministrazione-centrale@certunipv.it

Data di conseguimento della laurea: 27/07/1984

Luogo ed numero di iscrizione all'Ordine Professionale: Ordine dei Medici Chirurgi della Provincia di Pavia N.6766

Data di iscrizione all'Ordine Professionale: 25/10/1994

Specializzazione: specializzazione conseguita in Italia - Medicina Fisica e Riabilitativa

Università (completa di indirizzo/pec) presso cui ha conseguito la specializzazione: Università degli Studi di Pavia Indirizzo: Corso Strada Nuova 65, 27100 Pavia; PEC : amministrazione-centrale@certunipv.it

Data di conseguimento della specializzazione: 13/07/1987

Anzianità di servizio: 10 anni di servizio nella disciplina a concorso

Attestato di formazione manageriale: si, lo HO conseguito (allegare il certificato)

Data di conseguimento dell'attestato di formazione manageriale: 22/12/2017

Giudicati in procedimenti a proprio carico: ASSENZA a proprio carico di provvedimenti definitivi di accoglimento della domanda risarcitoria proposta dal danneggiato, passati in giudicato negli ultimi 3 anni rispetto alla data di pubblicazione del presente bando

**ULTERIORI SPECIALIZZAZIONI**

Specializzazione in Medicina dello Sport
conseguita presso Università degli Studi di Messina (indirizzo: Piazza Pugliatti 1 98122 Messina PEC: protocollo@pec.unime.it) il 26/10/1993

**TIPOLOGIA DELLE ISTITUZIONI**

Istituzione: Fondazione IRCCS Policlinico San Matteo (Indirizzo: Viale Golgi 19 27100 Pavia)
Tipologia: Istituto di Ricovero e Cura a Carattere Scientifico di Diritto Pubblico

**POSIZIONE FUNZIONALE**

Dal 01/09/2017 al 22/03/2023
dipendente a tempo indeterminato a rapporto esclusivo dirigente medico (disciplina medicina fisica e riabilitazione) presso FONDAZIONE IRCCS Policlinico San Matteo Pavia (indirizzo protocollo@pec.smatteo.pv.it) (pubblica amministrazione) a tempo pieno (n. 37,4 ore/sett.) - Posizione

funzionale: responsabile struttura semplice dipartimentale - Competenze: Struttura Semplice Dipartimentale Medicina Fisica e Riabilitazione. responsabilità sia per la gestione degli aspetti professionali specifici e sia la gestione del personale e delle altre risorse materiali affidate alla struttura per il raggiungimento degli obiettivi qualitativi e quantitativi prefissati - Causa di cessazione: nessuna, posizione ancora in corso

Dal 10/11/2016 al 31/08/2017
dipendente a tempo indeterminato a rapporto esclusivo dirigente medico (disciplina medicina fisica e riabilitazione) presso FONDAZIONE IRCCS Policlinico San Matteo Pavia (indirizzo protocollo@pec.smatteo.pv.it) (pubblica amministrazione) a tempo pieno (n. 37,4 ore/sett.) - Posizione funzionale: incarico di direttore struttura complessa facente funzione - Competenze: Struttura Complessa Medicina Fisica e Riabilitazione - Causa di cessazione: altro (specificare) passaggio ad altra posizione

Dal 01/05/2010 al 31/08/2017
dipendente a tempo indeterminato a rapporto esclusivo dirigente medico (disciplina medicina fisica e riabilitazione) presso FONDAZIONE IRCCS Policlinico San Matteo Pavia (indirizzo protocollo@pec.smatteo.pv.it) (pubblica amministrazione) a tempo pieno (n. 37,4 ore/sett.) - Posizione funzionale: incarico di alta specializzazione - Competenze: incarico di alta specializzazione denominata "Riabilitazione specialistica dipartimentale emergenza urgenza" della Struttura complessa Medicina Fisica e Riabilitazione. Si è occupato della programmazione e della organizzazione delle attività riabilitative nei reparti dipartimentali in essere. Ha svolto attività di consulenza riabilitativa ospedaliera prevalentemente nei reparti di ortopedia, di traumatologia, di week surgery e di neurochirurgia. Ha continuato a partecipare all'attività ordinaria divisionale della struttura Complessa di appartenenza. Ha svolto attività di tutoraggio per i medici in formazione specialistica in medicina fisica e riabilitativa. - Causa di cessazione: altro (specificare) passaggio ad altra posizione

Dal 01/07/2003 al 30/04/2010
dipendente a tempo indeterminato a rapporto esclusivo dirigente medico (disciplina medicina fisica e riabilitazione) presso FONDAZIONE IRCCS Policlinico San Matteo Pavia (indirizzo protocollo@pec.smatteo.pv.it) (pubblica amministrazione) a tempo pieno (n. 37,4 ore/sett.) - Posizione funzionale: incarico di natura professionale o di base - Competenze: Struttura Complessa Medicina Fisica e Riabilitazione - Causa di cessazione: altro (specificare)

Dal 01/01/1994 al 01/07/2003
dipendente a tempo indeterminato a rapporto esclusivo dirigente medico (disciplina medicina fisica e riabilitazione) presso FONDAZIONE IRCCS Policlinico San Matteo Pavia (indirizzo protocollo@pec.smatteo.pv.it) (pubblica amministrazione) a tempo pieno (n. 37,4 ore/sett.) - Posizione funzionale: nessun incarico - Competenze: struttura complessa Medicina Fisica e Riabilitazione - Causa di cessazione: altro (specificare) passaggio ad altra posizione

Dal 20/08/1990 al 31/12/1993
dipendente a tempo determinato a rapporto non esclusivo dirigente medico (disciplina medicina fisica e riabilitazione) presso FONDAZIONE IRCCS Policlinico San Matteo Pavia (indirizzo protocollo@pec.smatteo.pv.it) (pubblica amministrazione) a tempo definito (n. 28,3 ore/sett.) - Posizione funzionale: nessun incarico - Competenze: struttura complessa medicina fisica e riabilitazione - Causa di cessazione: altro (specificare) passaggio ad altra posizione

Dal 01/03/1989 al 30/06/1990
specialista ambulatoriale (SAI) a tempo determinato dirigente medico (disciplina medicina fisica e riabilitazione) presso ASL MI 2 Melegnano (indirizzo protocollo@pec.asst-melegnano-martesana.it) (pubblica amministrazione) a part time (n. 12 ore/sett.) - Posizione funzionale: nessun incarico - Causa di cessazione: scadenza del contratto a tempo determinato

Dal 01/04/1988 al 30/04/1989
specialista ambulatoriale (SAI) a tempo determinato dirigente medico (disciplina medicina fisica e riabilitazione) presso ASL Casale Monferrato (AL) (indirizzo aslal@pec.aslal.it) (pubblica amministrazione) a tempo definito (n. 10 ore/sett.) - Posizione funzionale: nessun incarico - Causa di cessazione: scadenza del contratto a tempo determinato

**TIPOLOGIA E QUANTITA' DELLE PRESTAZIONI**

Casistica presso IRCCS Policlinico San Matteo (indirizzo: viale Golgi 19, 27100 Pavia)

**SCHEDA RIEPILOGATIVA CASISTICA INDIVIDUALE**

Allego la scheda riepilogativa della casistica individuale

**ATTIVITA' DIDATTICA ACCADEMICA**

Anno accademico 1996/1997
Materia: massoterapia (titolo del corso: diploma laurea in fisioterapia) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 1997/1998
Materia: fisioterapia speciale (titolo del corso: diploma laurea fisioterapia) - Ente organizzatore: università di Pavia (indirizzo: amministtrazion-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 1998/1999
Materia: rieducazione disordini ATM e patologia rachidea (titolo del corso: diploma laurea fisioterapia) - Ente organizzatore: università di pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 1000 ore di docenza

Anno accademico 1999/2000
Materia: rieducazione disordini ATM e patologia rachidea (titolo del corso: diploma laurea fisioterapia) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2000/2001
Materia: rieducazione disordini ATM e patologia rachidea (titolo del corso: diplomalaurea fisioterapia) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2001/2002
Materia: rieducazione disordini ATM e patologia rachidea (titolo del corso: diploma laurea fisioterapia) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2002/2003
Materia: rieducazione disordini ATM e paologia rachidea (titolo del corso: diploma laurea fisioterapia) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2003/2004
Materia: rieducazione disordini ATM e paologia rachidea (titolo del corso: diplomalaurea fisioterapia) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2004/2005
Materia: rieducazione disordini ATM e paologia rachidea (titolo del corso: laurea in fisioterapia) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2005/2006
Materia: rieducazione disordini ATM e paologia rachidea (titolo del corso: laurea fisioterapia) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2006/2007
Materia: rieducazione disordini ATM e paologia rachidea (titolo del corso: laurea fisioterapia) - Ente organizzatore: università di Pavia (indirizzo: amministtrazion-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2007/2008
Materia: rieducazione disordini ATM e paologia rachidea (titolo del corso: laurea fisioterapia) - Ente organizzatore: università di Pavia (indirizzo: amministtrazion-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2008/2009
Materia: rieducazione disordini ATM e paologia rachidea (titolo del corso: laurea fisioterapia) - Ente organizzatore: università di Pavia (indirizzo: amministtrazion-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2009/2010
Materia: rieducazione disordini ATM e paologia rachidea (titolo del corso: laurea fisioterapia) - Ente organizzatore: università di Pavia (indirizzo: amministtrazion-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2010/2011
Materia: rieducazione disordini ATM e paologia rachidea (titolo del corso: laurea fisioterapia) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2011/2012
Materia: rieducazione disordini ATM e paologia rachidea (titolo del corso: laurea fisioterapia) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2012/2013
Materia: rieducazione disordini ATM e paologia rachidea (titolo del corso: laurea fisioterapia) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2013/2014
Materia: rieducazione disordini ATM e paologia rachidea (titolo del corso: laurea fisioterapia) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2014/2015
Materia: rieducazione disordini ATM e paologia rachidea (titolo del corso: laurea fisioterapia) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2015/2016
Materia: rieducazione disordini ATM e paologia rachidea (titolo del corso: laurea fisioterapia) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2016/2017
Materia: rieducazione disordini ATM e paologia rachidea (titolo del corso: laurea fisioterapia) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2017/2018
Materia: rieducazione disordini ATM e paologia rachidea (titolo del corso: laurea fisioterapia) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2018/2019
Materia: rieducazione disordini ATM e paologia rachidea (titolo del corso: laurea fisioterapia) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2002/2003
Materia: terapia fisica (titolo del corso: laurea in scienze motorie) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 23,00 ore di docenza

Anno accademico 2003/2004
Materia: terapia fisica (titolo del corso: laurea scienze motorie) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 23,00 ore di docenza

Anno accademico 2004/2005
Materia: medicina fisica e riabilitativa 1 (titolo del corso: laurea magistrale scienze tecniche attività motoria prev e adattate) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 24,00 ore di docenza

Anno accademico 2005/2006
Materia: medicina fisica e riabilitativa 1 (titolo del corso: LM - SCIENZE E TECNICHE DELLE ATTIVITÀ MOTORIE PREVENTIVE E ADATTATE) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 24,00 ore di docenza

Anno accademico 2006/2007
Materia: medicina fisica e riabilitativa 1 (titolo del corso: LM - SCIENZE E TECNICHE DELLE ATTIVITÀ MOTORIE PREVENTIVE E ADATTATE) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 24,00 ore di docenza

Anno accademico 2006/2007
Materia: medicina fisica e riabilitativa 1 (titolo del corso: LM - SCIENZE E TECNICHE DELLE ATTIVITÀ MOTORIE PREVENTIVE E ADATTATE) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 24,00 ore di docenza

Anno accademico 2007/2008
Materia: medicina fisica e riabilitativa 1 (titolo del corso: LM - SCIENZE E TECNICHE DELLE ATTIVITÀ MOTORIE PREVENTIVE E ADATTATE) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 24,00 ore di docenza

Anno accademico 2008/2009
Materia: medicina fisica e riabilitatriva 1 (titolo del corso: LM - SCIENZE E TECNICHE DELLE ATTIVITÀ MOTORIE PREVENTIVE E ADATTATE) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 24,00 ore di docenza

Anno accademico 2009/2010

Materia: medicina fisica e riabilitatriva 1 (titolo del corso: LM - SCIENZE E TECNICHE DELLE ATTIVITÀ MOTORIE PREVENTIVE E ADATTATE) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 24,00 ore di docenza

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Anno accademico 2013/2014
Materia: medicina fisica e riabilitatriva (titolo del corso: LM - SCIENZE E TECNICHE DELLE ATTIVITÀ MOTORIE PREVENTIVE E ADATTATE) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 24,00 ore di docenza

Anno accademico 2013/2014
Materia: medicina fisica e riabilitatriva (titolo del corso: LM - SCIENZE E TECNICHE DELLE ATTIVITÀ MOTORIE PREVENTIVE E ADATTATE) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 24,00 ore di docenza

Anno accademico 2014/2015
Materia: medicina fisica e riabilitatriva (titolo del corso: LM - SCIENZE E TECNICHE DELLE ATTIVITÀ MOTORIE PREVENTIVE E ADATTATE) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 24,00 ore di docenza

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Anno accademico 2016/2017
Materia: medicina fisica e riabilitatriva (titolo del corso: LM - SCIENZE E TECNICHE DELLE ATTIVITÀ MOTORIE PREVENTIVE E ADATTATE) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 24,00 ore di docenza

Anno accademico 2017/2018
Materia: medicina fisica e riabilitatriva (titolo del corso: LM - SCIENZE E TECNICHE DELLE ATTIVITÀ MOTORIE PREVENTIVE E ADATTATE) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 24,00 ore di docenza

Anno accademico 2018/2019
Materia: medicina fisica e riabilitatriva (titolo del corso: LM - SCIENZE E TECNICHE DELLE ATTIVITÀ MOTORIE PREVENTIVE E ADATTATE) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 24,00 ore di docenza

Anno accademico 2007/2008
Materia: medicina fisica e riabilitatriva (titolo del corso: laurea igiene) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 16,00 ore di docenza

Anno accademico 2008/2009
Materia: medicina fisica e riabilitatriva (titolo del corso: laurea igiene dentale) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 16,00 ore di docenza

Anno accademico 2009/2010
Materia: medicina fisica e riabilitatriva (titolo del corso: laurea igiene dentale) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 16,00 ore di docenza

Anno accademico 2010/2011
Materia: medicina fisica e riabilitatriva (titolo del corso: Laurea - IGIENE DENTALE) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 16,00 ore di docenza

Anno accademico 2011/2012
Materia: medicina fisica e riabilitatriva (titolo del corso: Laurea - IGIENE DENTALE) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 16,00 ore di docenza

Anno accademico 2012/2013
Materia: medicina fisica e riabilitatriva (titolo del corso: Laurea - IGIENE DENTALE) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 16,00 ore di docenza

Anno accademico 2013/2014
Materia: medicina fisica e riabilitatriva (titolo del corso: Laurea - IGIENE DENTALE) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 16,00 ore di docenza

Anno accademico 2014/2015
Materia: medicina fisica e riabilitatriva (titolo del corso: Laurea - IGIENE DENTALE) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 16,00 ore di docenza

Anno accademico 2015/2016
Materia: medicina fisica e riabilitatriva (titolo del corso: Laurea - IGIENE DENTALE) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 16,00 ore di docenza

Anno accademico 2016/2017
Materia: medicina fisica e riabilitatriva (titolo del corso: Laurea - IGIENE DENTALE) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 16,00 ore di docenza

Anno accademico 2017/2018
Materia: medicina fisica e riabilitatriva (titolo del corso: Laurea - IGIENE DENTALE) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 16,00 ore di docenza

Anno accademico 2018/2019
Materia: medicina fisica e riabilitatriva (titolo del corso: Laurea - IGIENE DENTALE) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 16,00 ore di docenza

Anno accademico 2019/2020
Materia: medicina fisica e riabilitatriva (titolo del corso: Laurea - IGIENE DENTALE) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 16,00 ore di docenza

Anno accademico 2020/2021
Materia: medicina fisica e riabilitatriva (titolo del corso: Laurea - IGIENE DENTALE) - Ente organizzatore: università di Pavia (indirizzo:

amministrazione-centrale@certunipv.it) - N. 16,00 ore di docenza

Anno accademico 2021/2022
Materia: medicina fisica e riabilitatriva (titolo del corso: Laurea - IGIENE DENTALE) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 16,00 ore di docenza

Anno accademico 1999/2000
Materia: trattamento riabilitativo scoliosi (titolo del corso: scuola specializzazione medicina fisica e riabilitazione) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2000/2001
Materia: trattamento riabilitativo scoliosi (titolo del corso: specializzazione medicina fisica e riabilitativa) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2001/2002
Materia: medicina manuale (titolo del corso: specializzazione medicina fisica e riabilitativa) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2002/2003
Materia: medicina manuale (titolo del corso: specializzazione medicina fisica e riabilitativa) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2003/2004
Materia: rieducazione disordini ATM (titolo del corso: specializzazione medicina fisica e riabilitativa) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2004/2005
Materia: medicina manuale (titolo del corso: specializzazione medicina fisica e riabilitativa) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2004/2005
Materia: patologia del rachide (titolo del corso: specializzazione medicina fisica e riabilitativa) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2005/2006
Materia: patologia del rachide (titolo del corso: specializzazione medicina fisica e riabilitativa) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2006/2007
Materia: patologia del rachide (titolo del corso: specializzazione medicina fisica e riabilitativa) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2007/2008
Materia: patologia del rachide (titolo del corso: specializzazione medicina fisica e riabilitativa) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2008/2009
Materia: patologia del rachide (titolo del corso: specializzazione medicina fisica e riabilitativa) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2009/2010
Materia: patologia del rachide (titolo del corso: specializzazione medicina fisica e riabilitativa) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2010/2011
Materia: patologia del rachide (titolo del corso: specializzazione medicina fisica e riabilitativa) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2011/2012
Materia: patologia del rachide (titolo del corso: specializzazione medicina fisica e riabilitativa) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2012/2013
Materia: patologia del rachide (titolo del corso: specializzazione medicina fisica e riabilitativa) - Ente organizzatore: università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2013/2014
Materia: medicina manuale (titolo del corso: specializzazione medicina fisica e riabilitazione) - Ente organizzatore: Università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2014/2015
Materia: medicina manuale (titolo del corso: scuola di specializzazione Medicina Fisica e Riabilitativa) - Ente organizzatore: Università di Pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2015/2016
Materia: tecniche di taping in riabilitazione (titolo del corso: specializzazione Medicina Fisica e Riabilitativa) - Ente organizzatore: Università di pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2016/2017
Materia: riabilitazione paziente con osteoporosi (titolo del corso: specializzazione Medicina Fisica e Riabilitativa) - Ente organizzatore: Università di pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2016/2017
Materia: Medicina Fisica e Riabilitativa (titolo del corso: Specializzazione Medicina Fisica e Riabilitativa) - Ente organizzatore: Università di pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2004/2005
Materia: medicina manuale (titolo del corso: specializzazione Medicina dello Sport) - Ente organizzatore: Università di pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2005/2006
Materia: medicina manuale (titolo del corso: specializzazione Medicina dello Sport) - Ente organizzatore: Università di pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2006/2007
Materia: medicina manuale (titolo del corso: specializzazione Medicina dello Sport) - Ente organizzatore: Università di pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2007/2008
Materia: medicina manuale (titolo del corso: specializzazione Medicina dello Sport) - Ente organizzatore: Università di pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2008/2009
Materia: medicina manuale (titolo del corso: specializzazione Medicina dello Sport) - Ente organizzatore: Università di pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2009/2010
Materia: medicina manuale (titolo del corso: specializzazione Medicina dello Sport) - Ente organizzatore: Università di pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2004/2005
Materia: riabilitazione traumatologica e protesica (titolo del corso: specializzazione Ortopedia) - Ente organizzatore: Università di pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2005/2006
Materia: riabilitazione traumatologica e protesica (titolo del corso: specializzazione Ortopedia) - Ente organizzatore: Università di pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2006/2007
Materia: riabilitazione traumatologica e protesica (titolo del corso: specializzazione Ortopedia) - Ente organizzatore: Università di pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2007/2008
Materia: riabilitazione traumatologica e protesica (titolo del corso: specializzazione Ortopedia) - Ente organizzatore: Università di pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2008/2009
Materia: riabilitazione traumatologica e protesica (titolo del corso: specializzazione Ortopedia) - Ente organizzatore: Università di pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

Anno accademico 2009/2010
Materia: riabilitazione traumatologica e protesica (titolo del corso: specializzazione Ortopedia) - Ente organizzatore: Università di pavia (indirizzo: amministrazione-centrale@certunipv.it) - N. 10,00 ore di docenza

**CONGRESSI, CONVEGNI E SEMINARI**

Dal 27/09/2012 al 29/09/2012
Relatore al corso: Innovazioni e strategie convalidate in Ortopedia e Traumatologia - Ente organizzatore: SPLLOT (indirizzo: corso BramanteTorino) (0,30 ore)

Dal 24/05/2013 al 24/05/2013
Relatore al corso: forza e funzione - l'attività funzionale in riabilitazione nello sport - Ente organizzatore: Università di pavia (indirizzo: amministrazionecentrale@certunipv.it) (0,30 ore)

Dal 26/10/2013 al 26/10/2013
Relatore al corso: anziani: trucchi per restare giovani - Ente organizzatore: FMSI AMSD (indirizzo: ams.pavia@certfmsi.it) (0,30 ore)

Dal 15/11/2013 al 15/11/2013
Relatore al corso: le certificazioni medico legali - Ente organizzatore: ATS Pavia (indirizzo: Via indipendenza pavia) (0,30 ore)

Dal 18/10/2014 al 18/10/2014
Relatore al corso: ambiente e salute nel territorio provinciale pavese - Ente organizzatore: OMCEO - Pavia (indirizzo: via Gaffurio 15) (0,30 ore)

Dal 08/11/2014 al 08/11/2014
Relatore al corso: problematiche assicurative e di tutela del professionista - Ente organizzatore: OMCEO (indirizzo: via gaffurio 15 pavia) (0,30 ore)

Dal 24/10/2015 al 24/10/2015
Relatore al corso: Riabilitazione nei reparti per acuti - Ente organizzatore: università di Pavia (indirizzo: amministarzione-centrale@certunipv.it) (0,30 ore)

Dal 14/12/2015 al 14/12/2015
Relatore al corso: interventistica MSK ecoguidata - Ente organizzatore: Università di Pasvia (indirizzo: amministrazione-centrale@certunipv.it) (0,30 ore)

Dal 15/10/2016 al 15/10/2016
Relatore al corso: la prevenzione delle casdute nell'anziano come sfida del millennio - Ente organizzatore: FSM Maugeri (indirizzo: via Salvatore Maugeri 15 Pavia) (0,30 ore)

Dal 23/06/2017 al 23/06/2017
Relatore al corso: corso SIMFER 10-18 clinica in medicina manuale diagnosi e trattamento - Ente organizzatore: SIMFER (indirizzo: via Po 22 Roma) (0,30 ore)

Dal 24/02/2018 al 24/02/2018
Relatore al corso: medicina personalizzata in oncologia: passato, presente, futuro - Ente organizzatore: DIPO Pavia (indirizzo: viale Golgi 19 pavia) (0,30 ore)

Dal 05/10/2019 al 05/10/2019
Relatore al corso: disfunzioni pelviperineali: valutazione e trattamento riabilitativo del paviemnto pelvico - Ente organizzatore: IRCCS Pol San Matteo pavia (indirizzo: piazzale Golgi 2 Pavia) (0,30 ore)

Dal 18/09/2021 al 18/09/2021
Relatore al corso: L'intervento riabilitativo nel percorso diagnostico terapeutico dell'operata al seno - Ente organizzatore: IRCCS Pol San Matteo pavia (indirizzo: piazzale Golgi 2 Pavia) (0,30 ore)

Dal 03/11/2021 al 03/11/2021
Relatore al corso: sintomi depressivi e decadimento cognitivo: ruolo del MMg in collaborazione con neurologo - Ente organizzatore: OMCEO pavia (indirizzo: via gaffurio 15 pavia) (0,30 ore)

Dal 25/03/2022 al 25/03/2022
Relatore al corso: tumori femminili prevenzione cura e ricerca - Ente organizzatore: DIPO Pavia (indirizzo: viale Golgi 19 pavia) (0,30 ore)

Dal 29/05/2022 al 31/05/2022
Relatore al corso: il cambiamento climatico. Interdisciplinità, un cambio di apradigma nella visione onehealth - Ente organizzatore: ISDE (indirizzo: via XXV Aprile 34 Arezzo) (0,30 ore)

**ATTIVITA' SCIENTIFICA E DI RICERCA**

Dal 09/04/2019 al 21/12/2022
Partecipazione in qualità di ricercatore coresponsabile - Tipo attività: osservazionale multicentrico - Titolo: Monitoraggio del paziente con stroke ischemico grazie allutilizzo di nuovi biomarcatori sierici e di imaging MRI - Ente di riferimento: ICS Maugeri IRCCS (indirizzo: responsabileprotezionedati@pecicsmaugeri.it)

Dal 05/12/2019 al 22/12/2022
Partecipazione in qualità di ricercatore - Tipo attività: osservazionale - Titolo: valutazione efficacia di un esercizio specifico sulle artromialgie mani e piedi indotte da terapia con inibitori aromatasi in pazienti operate per neoplasia della mammella. studio clinico controllato randomizzato in cieco singolo - Ente di riferimento: IRCCS Policlinico San Matteo Pavia (indirizzo: protocollo@pec.smatteo.pv.it)

Dal 05/12/2019 al 21/12/2022
Partecipazione in qualità di ricercatore - Tipo attività: osservazionale - Titolo: Valutazione della variazione del controllo posturale con pedana stabilometrica in pazienti affetti da lombalgia cronica, trattati con due differenti programmi di esercizi terapeutici/riabilitativi osservazionale - Ente di riferimento: IRCCS Policlinico San Matteo Pavia (indirizzo: protocollo@pec.smatteo.pv.it)

Dal 01/07/2009 al 01/07/2014
Partecipazione in qualità di ricercatore responsabile - Tipo attività: osservazionale - Titolo: Utilizzo dei fattori di crescita piastrinici autologhi nel trattamento dellartrosi di ginocchio in stadio II/III. - Ente di riferimento: IRCCS Policlinico San Matteo Pavia (indirizzo: protocollo@pec.smatteo.pv.it)

Dal 01/07/2008 al 01/07/2012
Partecipazione in qualità di ricercatore responsabile - Tipo attività: osservazionale - Titolo: Validazione di metodiche di approccio clinico e strumentale nella artropatia emofilica. - Ente di riferimento: IRCCS Policlinico San Matteo Pavia (indirizzo: protocollo@pec.smatteo.pv.it)

Dal 09/04/2013 al 28/02/2019
Partecipazione in qualità di ricercatore - Tipo attività: osservazionale - Titolo: Efficacia della terapia ad onde durto focalizzate nelle sindromi dolorose del gran trocantere. - Ente di riferimento: IRCCS Policlinico San Matteo Pavia (indirizzo: protocollo@pec.smatteo.pv.it)

Dal 11/08/2016 al 20/02/2019
Partecipazione in qualità di ricercatore - Tipo attività: osservazionale - Titolo: efficacia delle terapia ad onde d'urto focalizzate nella fascite plantare associata a sofferenza miofasciale del tricipite surale - Ente di riferimento: IRCCS Policlinico San Matteo Pavia (indirizzo: protocollo@pec.smatteo.pv.it)

Dal 06/08/2020 al 21/12/2021
Partecipazione in qualità di responsabile - Tipo attività: osservazionale - Titolo: riabilitazione in acuto e valutazione funzionale nel paziente COVID-19: dalla terapia intensiva alla dimissione - Ente di riferimento: IRCCS Policlinico San Matteo Pavia (indirizzo: protocollo@pec.smatteo.pv.it)

Dal 19/02/2021 al 31/12/2021
Partecipazione in qualità di responsabile - Tipo attività: osservazionale - Titolo: validazione italiania del questionario VISA-G nelle sindromi dolorose del gran trocantere - Ente di riferimento: IRCCS Policlinico San Matteo Pavia (indirizzo: protocollo@pec.smatteo.pv.it)

Dal 01/09/1988 al 30/08/1989
Partecipazione in qualità di ricercatore - Tipo attività: borsa di studio - Titolo: esercizio terapeutico - Ente di riferimento: Policlinico San Matteo (indirizzo: protocollo@pec.smatteo.pv.it)

Dal 01/09/1989 al 30/08/1990
Partecipazione in qualità di ricercatore - Tipo attività: borsa di studio - Titolo: valutazione funzionale con strumentazione isocinetica - Ente di riferimento: Policlinico San Matteo Pavia (indirizzo: protocollo@pec.smatteo.pv.it)

**PRODUZIONE SCIENTIFICA COMPLESSIVA**

- POSTER/comunicazioni n. 0
Produzione scientifica complessiva: ARTICOLI in extenso n. 9 con impact factor, n. 17 senza impact factor - CAPITOLI di libro/libri n. 1 nazionali, n. 0 internazionali - ABSTRACT n. 0 con impact factor, n. 0 senza impact factor

**PRODUZIONE SCIENTIFICA SIGNIFICATIVA**

Articolo in extenso
Rehabilitation and functional recovery after masseteric-facial nerve anastomosis. - pubblicato il 2016 - con IF (IF 1.827)

Articolo in extenso
Interobserver reliability of ultrasound assessment of haemophilic arthropathy: radiologist vs. non-radiologist. - pubblicato il 2016 - con IF (IF 3.596)

Articolo in extenso
Focused extracorporeal shock wave therapy combined with supervised eccentric training for supraspinatus calcific tendinopathy - pubblicato il 2018 - con IF (IF 2.101)

Articolo in extenso
Management of Peripheral Neuropathies Study Group.Observational multicentric study on chronic sciatic pain: clinical data from 44 Italian centres - pubblicato il 2017 - con IF (IF 2.387)

Articolo in extenso
Treatment of knee osteoarthritis: platelet-derived growth factors vs. hyaluronic acid. A randomized controlled trial. - pubblicato il 2017 - con IF (IF 2.93)

Articolo in extenso
Focused extracorporeal shock wave therapy for greater trochanteric pain syndrome with gluteal tendinopathy: a randomized controlled trial. - pubblicato il 2019 - con IF (IF 2.599)

Articolo in extenso
Significance of serum Myostatin in hemodialysis patients. - pubblicato il 2019 - con IF (IF 1.913)

Articolo in extenso



[redacted]

Postural analisys in a pediatric cohort of patients with Ehlers-Danlos Syndrome a pilot study - pubblicato il 2020 - con IF (IF 1.312)

Articolo in extenso

Functional assessment and rehabilitation protocol in acute patients affected by SARS-CoV-2 infection hospitalized in the Intensive Care Unit and in the Medical Care Unit. - pubblicato il 2022 - con IF (IF 5.313)

**ALTRO**

socio SIMFER

Presidente Ordine dei Medici e Odontoiatri di Pavia

componente Task Force "Ambiente -salute" Ministero della Salute

socio AISP Associazione Italiana Studio Postura

Dal 09/11/2009 al 13/11/2009

scuola di ecocgrafia muscolo-scheletrica università degli studi Bologna

Dal 10/03/1989 al 12/03/1989

corso didattico 1° livello Medicina Manuale Ospedale Niguarda Milano

Dal 10/11/1989 al 12/11/1989

corso didattico 2° livello Medicina Manuale Ospedasle Niguarda Milano

affiliato FMSI Federazione Medica Sportiva Italiana

Consigliere A.M.S.D, Associazione Medico Sportiva Dilettantistica sez.Pavia

socio Fondatore ASF Associazione Specialisti Fisiatri

socio Associazione Medici per l'Ambiente - ISDE Italia

Manifesto il mio consenso affinché i dati forniti possano essere trattati nel rispetto del GDPR 679/2016 (Regolamento europeo in materia di protezione dei dati personali) per gli adempimenti connessi alla presente procedura, nonché all'eventuale procedura di assunzione.

Sono consapevole delle sanzioni penali nel caso di dichiarazioni non veritiere, di formazione o uso di atti falsi, richiamate dall'art.76 del D.P.R. 445/2000, attesta che le dichiarazioni contenute nella presente domanda sono sostitutive di certificazione ai sensi dell'art.46 del D.P.R. 445/2000.

Autorizzo la Fondazione IRCCS Policlinico San Matteo alla pubblicazione del mio curriculum sul sito www.sanmatteo.org – sezione concorsi, in ottemperanza agli obblighi di trasparenza previsti dall'art. 15 del D.Lgs. n. 502/92, così come modificato dalla legge 189/2012.

Dichiaro che le copie dei documenti allegati alla presente domanda sono conformi all'originale in mio possesso ai sensi dell'art. 19 del D.P.R. n. 445/2000.

Dichiaro di accettare incondizionatamente tutte le clausole e le condizioni contenute nel bando.

FIRMA [redacted]

Fondazione IRCCS
Policlinico San Matteo

Sistema Socio Sanitario
Regione Lombardia

LA DIREZIONE SANITARIA

Vista la richiesta del Dr. Claudio Lisi in data 17/03/2023 per il rilascio della certificazione di "Tipologia dell' Ente"
DICHIARA E CERTIFICA

= che la Fondazione I.R.C.C.S. Policlinico "San Matteo" è Istituto di Ricovero e Cura a Carattere Scientifico di Diritto Pubblico

- Policlinico convenzionato con l'Università di Pavia;
- Codice regionale 030 codice d'istituto 030924
- Sito in Viale Golgi n. 17. Pavia 27100 tel. 5011 e con un presidio ospedaliero sito in Via Felice Cavallotti n. 123,
- 27011 Belgioioso PV
- n. totale posti letto ordinari accreditati: 1015
- n. totale posti letto in day hospital: 59
- n. totale postazioni tecniche: 97 (BIC+MAC) + 17Dialisi + 25 Culle
- collocazione rete di emergenza EAS II livello

CARATTERISTICHE STRUTTURALI

DIREZIONE SANITARIA
DIREZIONE SCIENTIFICA
DIREZIONE AMMINISTRATIVA

**AREA MEDICA**

| | | 2013 | | 2014 | | 2015 | | 2016 | | 2017 | | 2018 | | 2019 | | 2020 | | 2021 | | 2022 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| C.d.C. | Unità Operativa | PL | DH | PL | DH | PL | DH | PL | DH | PL | DH | PL | DH | PL | DH | PL | DH | PL | DH | PL | DH |
| 08-1 | Cardiologia | 30 | 4 | 30 | 4 | 30 | 4 | 30 | 4 | 30 | 4 | 30 | 4 | 30 | 4 | 30 | 4 | 30 | 4 | 30 | 4 |
| 50-1 | Cardiologia Cure Intensive Coronariche | 6 | 0 | 6 | 0 | 6 | 0 | 6 | 0 | 6 | 0 | 6 | 0 | 6 | 0 | 6 | 0 | 6 | 0 | 6 | 0 |
| 18-1 | Ematologia e Trapianto Midollo Osseo | 44 | 9 | 44 | 9 | 44 | 9 | 44 | 3 | 44 | 9 | 44 | 9 | 44 | 3 | 44 | 3 | 44 | 3 | 44 | 3 |
| 24-1 | Malattie Infettive | 35 | 6 | 35 | 6 | 35 | 6 | 35 | 1 | 35 | 6 | 35 | 6 | 35 | 1 | 35 | 1 | 35 | 1 | 35 | 1 |
| 24-2 | Malattie Infettive e Tropicali | 24 | 6 | 24 | 6 | 24 | 6 | 24 | 1 | 24 | 6 | 24 | 6 | 24 | 1 | 24 | 1 | 24 | 1 | 24 | 1 |
| 26-1 | Medicina Generale 2 | 53 | 3 | 53 | 3 | 53 | 3 | 53 | 0 | 53 | 3 | 53 | 3 | 53 | 0 | 53 | 0 | 53 | 0 | 53 | 0 |
| 26-2 | Medicina Generale 1 | 40 | 3 | 40 | 3 | 40 | 3 | 40 | 0 | 40 | 3 | 40 | 3 | 40 | 0 | 40 | 0 | 40 | 0 | 40 | 0 |
| 26-3 | Medicina Generale 3 | 20 | 0 | 20 | 0 | 20 | 0 | 20 | 0 | 20 | 0 | 20 | 0 | 20 | 0 | 20 | 0 | 20 | 0 | 20 | 0 |


| | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 64-1 | Oncologia Medica | 27 | 10 | 27 | 10 | 27 | 10 | 27 | 4 | 27 | 10 | 27 | 10 | 27 | 4 | 27 | 4 | 27 | 4 | 27 | 4 |
| 26-4 | Presidio Belgioioso – Cure Subacute | 27 | 4 | 27 | 4 | 27 | 4 | 20 | 0 | 27 | 4 | 27 | 4 | 20 | 0 | 20 | 0 | 20 | 0 | 20 | 0 |
| 99-1 | Presidio Belgioioso – Cure Palliative | 10 | 2 | 10 | 2 | 10 | 2 | 10 | 2 | 10 | 2 | 10 | 2 | 10 | 2 | 10 | 2 | 10 | 2 | 10 | 2 |
| 31-1 | Patologia Neonatale / Neonatologia Posti Tecnici | 25 | 0 | 25 | 0 | 25 | 0 | 25 | 0 | 25 | 0 | 25 | 0 | 25 | 0 | 25 | 0 | 25 | 0 | 25 | 0 |
| 62-1 | Patologia Neonatale / Terapia Intensiva | 45 | 0 | 45 | 0 | 45 | 0 | 34 | 0 | 45 | 0 | 45 | 0 | 45 | 0 | 45 | 0 | 45 | 0 | 34 | 0 |
| 39-1 | Clinica Pediatrica | 26 | 6 | 26 | 6 | 26 | 6 | 26 | 0 | 26 | 6 | 26 | 6 | 26 | 0 | 26 | 0 | 26 | 0 | 26 | 0 |
| 65-1 | Oncoematologia Pediatrica | 20 | 12 | 20 | 12 | 20 | 12 | 20 | 8 | 20 | 12 | 20 | 12 | 20 | 8 | 20 | 8 | 20 | 8 | 20 | 8 |
| 48-1 | Unità Operativa di Nefrologia | 16 | 2 | 16 | 2 | 16 | 2 | 16 | 0 | 16 | 2 | 16 | 2 | 16 | 0 | 16 | 0 | 16 | 0 | 16 | 0 |
| 71-1 | Unità Operativa di Reumatologia | 10 | 5 | 10 | 5 | 10 | 5 | 10 | 2 | 10 | 5 | 10 | 5 | 10 | 2 | 10 | 2 | 10 | 2 | 10 | 2 |
| 52-1 | Dermatologia | 26 | 6 | 26 | 6 | 26 | 6 | 26 | 2 | 26 | 6 | 26 | 6 | 26 | 2 | 26 | 2 | 26 | 2 | 26 | 2 |
| 68-1 | Malattie Apparato Respiratorio | 60 | 8 | 60 | 8 | 60 | 8 | 60 | 6 | 60 | 8 | 60 | 8 | 60 | 6 | 60 | 6 | 60 | 6 | 60 | 6 |
| 51-1 | Accettazione e P.S. Posti Tecnici OBI | 4 | 0 | 4 | 0 | 4 | 0 | 9 | 0 | 4 | 0 | 4 | 0 | 4 | 0 | 4 | 0 | 9 | 0 | 9 | 0 |
| 54-1 | Dialisi – Posti Tecnici | 13 | 0 | 13 | 0 | 13 | 0 | 17 | 0 | 13 | 0 | 13 | 0 | 13 | 0 | 13 | 0 | 17 | 0 | 17 | 0 |
| 58-1 | Medicina 6 - Ecografia Interventistica | 2 | 0 | 2 | 0 | 2 | 0 | 2 | 0 | 2 | 0 | 2 | 0 | 2 | 0 | 2 | 0 | 2 | 0 | 2 | 0 |

**AREA CHIRURGICA**

| | | 2013 | | 2014 | | 2015 | | 2016 | | 2017 | | 2018 | | 2019 | | 2020 | | 2021 | | 2022 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| C.d.C | Unità Operativa | PL | DH | PL | DH | PL | DH | PL | DH | PL | DH | PL | DH | PL | DH | PL | DH | PL | DH | PL | DH |
| 13-1 | Chirurgia Generale e Toracica | 27 | 0 | 27 | 0 | 27 | 0 | 4 | 0 | 27 | 0 | 4 | 0 | 4 | 0 | 4 | 0 | 4 | 0 | 4 | 0 |
| 09-2 | Chirurgia Generale 1 | 61 | 4 | 61 | 4 | 61 | 4 | 50 | 2 | 61 | 4 | 61 | 4 | 61 | 4 | 61 | 4 | 50 | 4 | 50 | 2 |
| 09-3 | Chirurgia Generale 2 | 42 | 4 | 42 | 4 | 42 | 4 | 50 | 2 | 42 | 4 | 42 | 4 | 42 | 4 | 42 | 4 | 50 | 4 | 50 | 2 |
| 43-1 | Urologia | 27 | 2 | 27 | 2 | 27 | 2 | 27 | 1 | 27 | 2 | 27 | 2 | 27 | 1 | 27 | 1 | 27 | 1 | 27 | 1 |
| 36-1 | Ortopedia e Traumatologia | 57 | 3 | 57 | 3 | 57 | 3 | 75 | 0 | 57 | 3 | 75 | 3 | 75 | 0 | 75 | 0 | 75 | 0 | 75 | 0 |
| 36-2 | Traumatologia | 40 | 0 | 40 | 0 | 40 | 0 | 0 | 0 | 40 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 14-1 | Chirurgia Vascolare | 30 | 0 | 30 | 0 | 30 | 0 | 26 | 0 | 30 | 0 | 30 | 0 | 30 | 0 | 30 | 0 | 26 | 0 | 26 | 0 |
| 30-1 | Neurochirurgia e Sezione di Unità Spinale | 28 | 1 | 28 | 1 | 28 | 1 | 28 | 1 | 28 | 1 | 28 | 1 | 28 | 1 | 28 | 1 | 28 | 1 | 28 | 1 |
| 11-1 | Chirurgia Pediatrica | 24 | 1 | 24 | 1 | 24 | 1 | 24 | 1 | 24 | 1 | 24 | 1 | 24 | 1 | 24 | 1 | 24 | 1 | 24 | 1 |
| 37-1 | Ostetricia e Ginecologia | 60 | 8 | 60 | 8 | 60 | 8 | 60 | 8 | 60 | 4 | 60 | 8 | 60 | 8 | 60 | 6 | 60 | 4 | 60 | 4 |
| 34-1 | Oculistica | 18 | 14 | 18 | 14 | 18 | 14 | 18 | 14 | 18 | 3 | 18 | 14 | 18 | 14 | 18 | 3 | 18 | 3 | 18 | 3 |


| | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 38-1 | Otorinolaringoiatria – Ch. MaxilloFacciale | 36 | 2 | 36 | 2 | 36 | 2 | 36 | 2 | 36 | 2 | 36 | 2 | 36 | 2 | 36 | 2 | 36 | 2 | 36 | 2 |
| 07-1 | Cardiochirurgia | 30 | 4 | 30 | 4 | 30 | 4 | 30 | 4 | 30 | 4 | 30 | 4 | 30 | 4 | 30 | 4 | 30 | 4 | 30 | 4 |
| 67-1 | Clinica Intra Moenia | 36 | 0 | 36 | 0 | 36 | 0 | 36 | 0 | 16 | 0 | 16 | 0 | 16 | 0 | 16 | 0 | 16 | 0 | 16 | 0 |

## AREA ODONTOIATRICA

| | | 2013 | | 2014 | | 2015 | | 2016 | | 2017 | | 2018 | | 2019 | | 2020 | | 2021 | | 2022 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| C.d.C. | Unità Operativa | PL | DH | PL | DH | PL | DH | PL | DH | PL | DH | PL | DH | PL | DH | PL | DH | PL | DH | PL | DH |
| 021110 | Clinica Odontoiatrica | 0 | *2 | 0 | *2 | 0 | *2 | 0 | *2 | 0 | *2 | 0 | *2 | 0 | *2 | 0 | *2 | 0 | 2 | 0 | 2 |

* : Posti ricompresi fra quelli del Day Hospital Polifunzionale fino al 2013

## AREA MEDICINA DIAGNOSTICA E DEI SERVIZI

| | | 2013 | | 2014 | | 2015 | | 2016 | | 2017 | | 2018 | | 2019 | | 2020 | | 2021 | | 2022 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| C.d.C | Unità Operativa | PL | DH | PL | DH | PL | DH | PL | DH | PL | DH | PL | DH | PL | DH | PL | DH | PL | DH | PL | DH |
| 490110 | Anestesia e Rianimazione 1 | 9 | 0 | 9 | 0 | 9 | 0 | 9 | 0 | 9 | 0 | 9 | 0 | 9 | 0 | 9 | 0 | 9 | 0 | 12 | 0 |
| 490210 | Anestesia e Rianimazione 2 | 10 | 0 | 10 | 0 | 10 | 0 | 10 | 0 | 10 | 0 | 10 | 0 | 10 | 0 | 10 | 0 | 10 | 0 | 10 | 0 |
| 490310 | Anestesia e Rianimazione 3 | 12 | 0 | 12 | 0 | 12 | 0 | 12 | 0 | 12 | 0 | 12 | 0 | 12 | 0 | 12 | 0 | 12 | 0 | 9 | 0 |
| 693110 | Radiologia e Terapia Fisica | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 693210 | Radiodiagnostica | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 743110 | Radioterapia Oncologica | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 803271 | Analisi Chimico Cliniche | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 803110 | Analisi Microbiologiche | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 183310 | Immunoematologia e Trasfusione | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 033170 | Anatomia e Istologia Patologica | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 803371 | Virologia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 273110 | Medicina Legale | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 693160 | Medicina Nucleare | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 563110 | Recupero e Rieducazione Funzionale | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 583210 | Endoscopia Digestiva | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

## AREA DI FARMACIA

Fondazione IRCCS
Policlinico San Matteo

Sistema Socio Sanitario
Regione
Lombardia

| | | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 553110 | Struttura di Farmacia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

SERVIZI DI PARTICOLARE RILEVANZA SPECIALISTICA

- Laboratori Sperimentali di ricerca:
  - Area Infettivologica
  - Area Trapiantologica
  - Area di Tecnologie Biomediche e Biotecnologie
  - Area Informatica Medica e Modelli Gestionali
- Fisica Sanitaria

Pavia li, 17/03/2023

IL DIRETTORE MEDICO DI PRESIDIO

[redacted]

Fondazione IRCCS
Policlinico San Matteo

Sistema Socio Sanitario
Regione Lombardia

**U.O.C. DIREZIONE MEDICA DI PRESIDIO**

Direttore
Dr. Carlo Marena

Tel. 0382 503415 - 503419
Fax 0382 503540

direzionemedicapresidio@smatteo.pv.it

TIPOLOGIA QUALITATIVA E QUANTITATIVA DELLE PRESTAZIONI

effettuate dal candidato Claudio Lisi negli anni di Servizio (2013_2022)

Si dichiara che il Dott. **Claudio lisi**

nato a [redacted]

assegnato alla STRUTTURA SEMPLICE DIPARTIMENTALE DI RIABILITAZIONE SPECIALISTICA -DIPARTIMENTO MEDICINA -FONDAZIONE IRCCS POLICLINICO "SAN MATTEO"

In relazione all'attività degli ultimi 10 anni presso la U.O. di Riabilitazione Specialistica, diretta:

dal 01/01/2013 al 01/09/2016 come S.C. di Riabilitazione e Recupero Funzionale dalla Prof.ssa Elena Dalla Toffola

dal 10/11/2016 al 31/08/2017 come S.C. di Riabilitazione e Recupero Funzionale dal Dott. Lisi Claudio Incarico di Direttore f.f.

Dal 01/09/2017 a tutt'oggi come U.O.S.D. di Riabilitazione Specialistica dal Dott Lisi Claudio Responsabile di Struttura Semplice Dipartimentale

ha svolto nel periodo dal 01.01.2012 ad oggi le seguenti attività:

**dal 01.01.213 al 30/04/2013 come Incarico di posizione dirigenziale di natura professionale**

Ha svolto attività ambulatoriale divisionale disponendo la stesura di piani di trattamento riabilitativo sulla base della valutazione di diversi tipologie di menomazioni e disabilità (conseguenti in proporzioni circa equivalenti a: patologia degenerativa od infiammatoria dell'apparato locomotore, esiti di interventi ortopedico-traumatologici, patologia neurologica) e disponendo inoltre l'opportuna terapia fisica strumentale e farmacologica.

E' responsabile dell'ambulatorio specialistico scoliosi

E' responsabile dell'Ambulatorio specialistico" disturbi Articolazione Temporomandibolare e rachide "

Ha svolto attività di consulenza interna nei reparti: Cl. Ortopedica e Traumatologica I e II: in cui si è occupato di rieducazione delle menomazioni motorie conseguenti ad interventi relativi a fatti traumatici, a grave patologia degenerativa dell'apparato locomotore, a chirurgia protesica articolare.

Chirurgia Vascolare: in cui si è occupato di rieducazione di fatti ischemici acuti, di rieducazione dei linfedemi e vascolare, di rieducazione precoce dell'amputato

Neurochirurgia: in cui si è occupato di rieducazione delle menomazioni motorie conseguenti alla patologia neurochirurgica di base, sia centrale, quale l'asportazione di espansi intracranici od i traumi cranici, sia periferica quale l'asportazione di ernie discali cervicali o lombari.

**Dal 01/05/2013 e sino al 10/11/2016** ha avuto tipologia di **incarico di alta specializzazione** denominata "Riabilitazione specialistica dipartimentale emergenza urgenza"

Per questo incarico ha svolto, in rapporto delle funzioni prescritte dell'incarico stesso, specifici compiti. Si è occupato della programmazione e della organizzazione delle attività riabilitative nei reparti dipartimentali in essere. Ha svolto attività di consulenza riabilitativa ospedaliera prevalentemente nei reparti di ortopedia, di traumatologia, di week surgery.

Ha collaborato alla stesura e alla attivazione dei progetti FAST-TRACK per i pazienti ricoverati e sottoposti ad intervento chirurgico in elezione nei reparti di Ortopedia

In questi anni ha effettuato per anno circa 1500 consulenze di visita fisiatrica con stesura di Progetto Riabilitativo Individuale o prescrizione di presidi e ausili nei reparti di competenza

Ha continuato a partecipare all'attività ordinaria divisionale della struttura Complessa di appartenenza. Ha svolto attività di tutoraggio per i medici in formazione specialistica in medicina fisica e riabilitativa. Ha proseguito la sua collaborazione nelle attività di ricerca scientifica. In tale periodo ha evidenziato ottima capacità di organizzazione e di coordinazione dell'attività del team, della stesura dei Progetti Riabilitativi e dei programmi riabilitativi; di stesura e prescrizione di ausili e ortesi. Ha dimostrato e confermato le sue conoscenze specifiche nell'utilizzo della strumentazione per la diagnosi e il trattamento di patologia in prevalenza in ambito muscoloscheletrico e nell'aggiornamento dei percorsi diagnostici terapeutici e riabilitativi. Ha eseguito trattamenti di medicina manuale prevalentemente del rachide, mesoterapia, terapia Dryneedling, terapia infiltrativa articolare con utilizzo anche dei fattori di crescita piastrinici oggetto di progetto ricerca.

FONDAZIONE IRCCS POLICLINICO - PAVIA -

In questi anni ha effettuato in media 1400 prime visite fisiatriche e visite fisiatriche di controllo; 250 prestazioni di altra tipologia (manipolazioni manu medica, infiltrazioni articolari, valutazione strumentale)

Ha collaborato nel gruppo multidisciplinare dell'emofilia per la valutazione della patologia muscoloscheletrica e per la presa in carico per trattamento riabilitativo. Tale patologia è oggetto di progetto di ricerca e di pubblicazione scientifica.

**Dal 10/11/2016 sino al 31/08/2017** ha avuto l'incarico di Direttore f.f. della Struttura Complessa di Riabilitazione e Recupero funzionale

Dal 01/09/2017 la struttura complessa di Riabilitazione e Recupero Funzionale è stata trasformata (come da POAS) in Struttura Semplice Dipartimentale UOSD Medicina Fisica e Riabilitazione.

**A far data del 01/09/2017 a tutt'oggi** il Dr Lisi ricopre l'incarico di posizione dirigenziale di Responsabile della Struttura Semplice Dipartimentale UOSD Medicina Fisica e Riabilitazione.

In questo periodo in qualità di responsabile si è occupato dei sistemi di governo clinico in termini di innovazione organizzativa e gestione finalizzati al miglioramento dei processi e dell'appropriatezza professionale; della gestione degli aspetti professionali specifici e della gestione del personale e delle altre risorse materiali affidate alla struttura per il raggiungimento degli obiettivi qualitativi e quantitativi prefissati Definizione dei percorsi assistenziali attraverso l'elaborazione dei PDTRA e in particolare in tempi recenti:

-percorso diagnostico terapeutico assistenziale per la gestione dei pazienti con tumori maligni del distretto testa collo

- Percorso diagnostico terapeutico per il trattamento riabilitativo del paziente con stroke i in fase acuta

- Percorso Diagnostico Terapeutico Riabilitativo Assistenziale per la gestione intraospedaliera dell'ictus

Percorso Diagnostico Terapeutico Riabilitativo Assistenziale per la gestione dei pazienti con polmonite acquisita in comunità

Percorso Diagnostico Terapeutico Riabilitativo Assistenziale per la gestione dei pazienti con patologia tumorale della mammella presso la Fondazione IRCCS Policlinico San Matteo

Revisione del PDTA paziente con tumore ereditario

Revisione del PDTA tumori del colon-retto

Per l'attività assistenziale si è occupato della gestione delle attività clinico assistenziali specifiche con particolare riguardo agli aspetti di programmazione dell'attività, della valutazione dei carichi di lavoro e delle prestazioni individuali dei collaboratori.

FONDAZIONE IRCCS POLICLINICO SAN M... [redacted]

Negli ultimi cinque anni, nello specifico, la sua attività assistenziale ha riguardato l'attività clinica diretta degli ambulatori specialistici "scoliosi", "patologia distretto cervicocraniomandibolare e rachide" sia l'attività nell' ambulatorio generale con il ruolo prevalentemente di supporto, controllo e supervisione.

Ha eseguito trattamenti di medicina manuale prevalentemente del rachide, mesoterapia, terapia Dryneedling, terapia infiltrativa articolare con utilizzo anche dei fattori di crescita piastrinici oggetto di progetto ricerca.)

attività ambulatoriale speciale

-Ambulatorio scoliosi: inquadramento diagnostico, stesura progetto riabilitativo, prescrizione protesica corsetti, collaudo corsetti, monitoraggio della congruità dei corsetti nel tempo di presa in carico, identificazione obiettivi ed esecuzione del programma riabilitativo da parte del fisioterapista della patologia vertebrale dell'età evolutiva.

-Ambulatorio disordini cranio mandibolari: inquadramento diagnostico, stesura progetto riabilitativo, identificazione obiettivi, trattamento manuale manu-medica dell'articolazione temporomandibolare nei blocchi articolari acuti e cronici, esecuzione del programma riabilitativo da parte del fisioterapista delle patologie dell'articolazione temporo-mandibolare.

L'attività di consulenza nei reparti è stata rivolta al supporto dei colleghi dell'U.O. e all'organizzazione del lavoro per il rispetto dei tempi di attuazione delle visite di consulenza, della stesura dei Progetti Riabilitativi individuali e dei programmi riabilitativi individuali per la corretta presa in carico da parte del personale di fisioterapia. Come da istruzioni operative la U.O. garantisce, come attività di consulenza dei reparti, l'attuazione delle visite fisiatriche entro le 24 ore per la successiva presa incarico, ove prevista, da parte del personale fisioterapista operativo nei singoli reparti.

In questi anni ha eseguito una media per anno di 500 tra prima visita fisiatrica e visita fisiatrica di controllo; 150 prestazioni di altra tipologia ( manipolazioni, manu medica, infiltrazioni articolari, valutazione strumentale

I valori descritti nelle tabelle sono in riferimento al ruolo svolto prima come dirigente di alta specializzazione dal 2012 al 2016, in seguito come Direttore f.f. della Struttura Complessa di Riabilitazione e Recupero funzionale e successivamente di Responsabile della Struttura Semplice Dipartimentale UOSD Medicina Fisica e Riabilitazione Responsabile dal 01/09/2017 ad oggi.

[redacted]

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[redacted]

Fondazione IRCCS Policlinico San Matteo

Istituto Socio Sanitario Regione Lombardia

# VISITE FISIATRICHE CONSULENZA REPARTI parte B

| DESCRIZIONE | CONSULENZE REPARTI | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 |
|---|---|---|---|---|---|---|---|---|---|
| VISITA DI FISIAT | Rianimazione II Cardiopolmonare | | 13 | 8 | 9 | 4 | 3 | | |
| VISITA DI FISIAT | Attivita di Cure Subacute - Pavia | | 15 | 12 | 16 | 10 | 7 | 6 | 4 |
| VISITA DI FISIAT | BELGIOIOSO REP.B DEGENTI | 1 | 2 | 5 | 7 | 4 | 4 | 2 | |
| VISITA DI FISIAT | CARD. CURE INT. CORONARICHE | | | | | 1 | | | |
| VISITA DI FISIAT | CARDIOCHIR. DEGENTI | | 2 | 1 | 10 | 2 | 7 | | |
| VISITA DI FISIAT | CARDIOLOGIA DEGENZA | 5 | 3 | 5 | 6 | 4 | 1 | | |
| VISITA DI FISIAT | CHIR. VASCOLARE DEGENTI | 6 | 8 | 3 | 14 | 9 | 12 | 4 | |
| VISITA DI FISIAT | Chirurgia Generale 1 Degenti A | 14 | 12 | 3 | 5 | 4 | 2 | | |
| VISITA DI FISIAT | Chirurgia Generale 1 Degenti B | 2 | 3 | 5 | 2 | 2 | 2 | 1 | |
| VISITA DI FISIAT | Chirurgia Generale 2 Degenti C | 3 | 4 | 5 | 4 | 3 | 2 | | |
| VISITA DI FISIAT | Chirurgia Generale 2 Degenti D | 5 | 1 | 3 | 12 | 3 | 2 | 1 | |
| VISITA DI FISIAT | Chirurgia Toracica Degenti | | 2 | 1 | 1 | 2 | 4 | | |
| VISITA DI FISIAT | Cure Palliative Degenti Belg. | 5 | 20 | 11 | 11 | 10 | 8 | | |
| VISITA DI FISIAT | EMATOLOGIA DEGENTI | 4 | 3 | 5 | 5 | 6 | 2 | | |
| VISITA DI FISIAT | Ginecologia Degenti (sez.22) | | | 1 | | 1 | 1 | | |
| VISITA DI FISIAT | INTRA MOENIA DEGENTI | 12 | 3 | 5 | 16 | 8 | 1 | | |
| VISITA DI FISIAT | MAL. INF.TROPICALI DEGENTI | 1 | | | | | | 1 | |
| VISITA DI FISIAT | MAL. INFETTIVE DEGENTI | 4 | 3 | 5 | 7 | 3 | | | |
| VISITA DI FISIAT | MALAT. APP. RESP - DEGENTI 3 | 1 | 1 | | 2 | | | | |
| VISITA DI FISIAT | MALAT. APP. RESPIRAT. DEGENTI 1 | 2 | 3 | 2 | 6 | 2 | | | |
| VISITA DI FISIAT | MALAT. APP. RESPIRAT. DEGENTI 2 | 2 | 3 | 2 | 3 | 2 | | | |
| VISITA DI FISIAT | MALAT. APP. RESPIRAT. TRAPIANTI | 2 | | | 1 | 4 | | | |
| VISITA DI FISIAT | Maxillo Facciale c/o ORL | 1 | 1 | 3 | 4 | 1 | | | |

FONDAZIONE IRCCS POLICLINICO SAN MATTEO - PAVIA - DIREZIONE MEDICA DI PRESIDIO

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Fondazione IRCCS Policlinico San Matteo

Istituto Sede Scientifica

Regione Lombardia

# VISITE FISIATRICHE DI CONSULENZA REPARTI parte A

| DESCRIZIONE | CONSULENZE REPARTI | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 |
|---|---|---|---|---|---|---|---|---|---|
| VISITA DI FISIAT | MED.1 M.I.O.M. REP.11 | 3 | 2 | 4 | 2 | 2 | 1 | | |
| VISITA DI FISIAT | MED.2 M.V. REP.19/19 BIS | 9 | 15 | 16 | 43 | 50 | 38 | 10 | |
| VISITA DI FISIAT | MED.3 REP.15 ex 14 DEG.ZA | | | 1 | | 1 | 2 | 2 | |
| VISITA DI FISIAT | Medicina Generale 1 | | | 1 | | | 1 | | |
| VISITA DI FISIAT | Medicina Generale 2 | | | | | 2 | 1 | | |
| VISITA DI FISIAT | Medicina Gen. Media Intensita | | | | 2 | 2 | | | |
| VISITA DI FISIAT | Medicina Vascolare | 28 | 33 | 24 | 22 | 28 | 18 | 16 | |
| VISITA DI FISIAT | NEFROLOGIA DEGENTI | | | | | 1 | 1 | | |
| VISITA DI FISIAT | NEUROCHIRURGIA DEGENTI | 12 | 17 | 12 | 15 | 15 | 14 | 8 | |
| VISITA DI FISIAT | OCULISTICA DEGENTI | | | | 1 | | | | |
| VISITA DI FISIAT | ONCOEMAT. PED. DEGENTI | 2 | 4 | 1 | 2 | 3 | 1 | | |
| VISITA DI FISIAT | Oncologia Degenti | | | 1 | | | | | |
| VISITA DI FISIAT | Ortopedia Degenti | | 170 | 341 | 407 | 331 | 251 | 19 | |
| VISITA DI FISIAT | Ortopedia degenti Lib Prof | | | | | | | 1 | |
| VISITA DI FISIAT | ORTOPEDIA REP.3 MASCHI | 375 | 223 | | | | | | |
| VISITA DI FISIAT | Ortopedia Week Surgery | 416 | 509 | 600 | 571 | 492 | 511 | 51 | 28 |
| VISITA DI FISIAT | OTORINOLARING. DEGENTI | 2 | 4 | 2 | 3 | 3 | 1 | | |
| VISITA DI FISIAT | PEDIATRIA DEGENTI (3 PIANO) | 6 | 8 | 6 | 4 | 5 | 3 | 1 | 1 |
| VISITA DI FISIAT | PEDIATRIA MAC | | | | | | 1 | | |
| VISITA DI FISIAT | Prericovero - Pediatria Univ. | | | | | 3 | | | |
| VISITA DI FISIAT | PSICHIATRIA DEGENTI | 1 | | | 1 | | | | |
| VISITA DI FISIAT | REUMATOLOGIA DEGENTI | | | | | 1 | 2 | | |
| VISITA DI FISIAT | RIANIMAZIONE I DEGENTI | | 2 | | 3 | 3 | | | |
| VISITA DI FISIAT | RIANIMAZIONE II DEGENTI | | 2 | | 6 | 1 | | | |
| VISITA DI FISIAT | Senologia Degenza | | | | | | 1 | | |
| VISITA DI FISIAT | Traumatologia | | 342 | 456 | 425 | 333 | 427 | 45 | 35 |
| VISITA DI FISIAT | TRAUMATOLOGIA DEGENTI | 317 | 236 | | | | | | |
| VISITA DI RIABIL | MED.2 M.V. REP.19/19 BIS | 3 | 1 | 4 | 6 | 3 | 2 | | |

FONDAZIONE IRCCS POLICLINICO SAN MATTEO - PAVIA - DIREZIONE MEDICA DI PRESIDIO

IL [redacted]

[redacted]

Fondazione IRCCS Policlinico San Matteo

Regione Lombardia

| ATTIVITA' AMBULATORIALI 2018-2022 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| CDC_EROG | ATTIVITA' AMBULATORIALE | PREST | PRESTAZIONI | 2018 | 2019 | 2020 | 2021 | 2022 |
| 563110 | Med Fisica e Riab. Amb. Divisionale | 8192 | INIEZIONE DI SOSTANZE TERAPEUTICHE | 34 | 40 | 18 | 5 | 13 |
| 563114 | Med Fisica e Riab. Amb. Scoliosi e disfunzioni temporo m | 8901 | VISITA DI CONTROLLO | 358 | 363 | 210 | 189 | 255 |
| 563110 | Med Fisica e Riab Amb. Divisionale | 8907 | VISITA MULTIDISCIPLINARE | | | | | 1 |
| 563110 | Med Fisica e Riab Amb. Divisionale | 89442 | TEST DEL CAMMINO | | | 1 | | |
| 563114 | Med Fisica e Riab Amb. Scoliosi e disfunzioni temporo ma | 897B2 | PRIMA VISITA MEDICINA FISICA E RIABILITAZION | 137 | 225 | 118 | 166 | 124 |
| 563110 | Med Fisica e Riab Amb. Divisionale | 9303 | VALUTAZIONE PROTESICA | 3 | 6 | 1 | 4 | 11 |
| 563114 | Med Fisica e Riab Amb. Scoliosi e disfunzioni temporo ma | 9303 | VALUTAZIONE PROTESICA | 34 | 40 | 18 | 5 | 13 |
| 563110 | Med Fisica e Riabilitazione Amb. Divisionale | 93054 | TEST POSTUROGRAFICO | 3 | 4 | | 1 | |
| 563110 | Med Fisica e Riab Amb. Divisionale | 93055 | TEST STABILOMETRICO STATICO DINAMICO | 3 | 69 | 10 | 10 | 34 |
| 563114 | Med Fisica e Riab Amb. Scoliosi e disfunzioni temporo ma | 93055 | TEST STABILOMETRICO STATICO DINAMICO | | 20 | 11 | 2 | |
| 563110 | Med Fisica e Riab Amb. Divisionale | 9315 | MOBILIZZAZIONE COLONNA VERTEBRALE | 20 | 30 | 15 | 6 | 13 |
| 563114 | Med Fisica e Riab Amb. Scoliosi e disfunzioni temporo ma | 9315 | MOBILIZZAZIONE COLONNA VERTEBRALE | | | | 3 | |
| 563110 | Med Fisica e Riabe Amb. Divisionale | 9316 | MOBILIZZAZIONE DI ALTRE ARTICOLAZIONI | 2 | 5 | | | 3 |
| 563114 | Med Fisica e Riab Amb. Scoliosi e disfunzioni temporo ma | 9316 | MOBILIZZAZIONE DI ALTRE ARTICOLAZIONI | | 2 | 9 | | |
| 563110 | Med Fisica e Riabilitazione Amb. Divisionale | 93351 | AGOPUNTURA CON MOXA REVULSIVANTE | | | | 3 | 8 |
| 563110 | Med Fisica e Riabilitazione Amb. Divisionale | 93564 | BENDAGGIO ADESIVO ELASTICO | | | 2 | | 10 |
| 563110 | Med Fisica e Riabilitazione Amb. Divisionale | 98591 | TERAPIA AD ONDE D'URTO FOCALIZZATE | 25 | 21 | 10 | 13 | 18 |
| 563114 | Med Fisica e Riab Amb. Scoliosi e disfunzioni temporo ma | 98591 | TERAPIA AD ONDE D'URTO FOCALIZZATE | | 3 | | | |
| 563110 | Med Fisica e Riabilitazione Amb. Divisionale | 99297 | MESOTERAPIA (inclusa antalgica) | 13 | 21 | 6 | 5 | 22 |
| 563114 | Med Fisica e Riab Amb. Scoliosi e disfunzioni temporo ma | 99991 | LASER TERAPIA ANTALGICA | 30 | 42 | 23 | 40 | 26 |

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FONDAZIONE IRCCS POLICLINICO SAN MATTEO
DIREZIONE MEDICA DI PRESIDIO
- PAVIA -

Fondazione IRCCS Policlinico San Matteo

Regione Lombardia

# ATTIVITA' AMBULATORIALI 2013-2017

| CDC_EROG | ATTIVITA' AMBULATORIALI | PREST | DESCR_BREVE | 2013 | 2014 | 2015 | 2016 | 2017 |
|---|---|---|---|---|---|---|---|---|
| 563110 | Med Fisica e Riab Amb. Divisionale | 897 | PRIMA VISITA | 386 | 379 | 373 | 421 | 398 |
| 563114 | Med Fisica e Riab Amb. Scoliosi e disfunzioni temporo ma | 897 | PRIMA VISITA | 60 | 37 | 60 | 72 | 131 |
| 563110 | Med Fisica e Riab Amb. Divisionale | 8192 | INIEZIONE DI SOSTANZE TERAPEUTICHE NELL'ARTICOL | 21 | 17 | 12 | 4 | 28 |
| 563110 | Med Fisica e Riab Amb. Divisionale | 8901 | VISITA DI CONTROLLO | 569 | 571 | 549 | 579 | 586 |
| 563114 | Med Fisica e Riab Amb. Scoliosi e disfunzioni temporo ma | 8901 | VISITA DI CONTROLLO | 298 | 349 | 409 | 405 | 538 |
| 563110 | Med Fisica e Riabilitazione Amb. Divisionale | 8907 | VISITA MULTIDISCIPLINARE | | 1 | | | |
| 563110 | Med Fisica e Riabilitazione Amb. Divisionale | 9303 | VALUTAZIONE PROTESICA | | | 2 | 2 | 1 |
| 563114 | Med Fisica e Riab Amb. Scoliosi e disfunzioni temporo ma | 9303 | VALUTAZIONE PROTESICA | 43 | 61 | 58 | 67 | 40 |
| 563110 | Med Fisica e Riabilitazione Amb. Divisionale | 9315 | MOBILIZZAZIONE DELLA COLONNA VERTEBRALE | 16 | 15 | 18 | 27 | 14 |
| 563114 | Med Fisica e Riab Amb. Scoliosi e disfunzioni temporo ma | 9315 | MOBILIZZAZIONE DELLA COLONNA VERTEBRALE | | | | 3 | 12 |
| 563114 | Med Fisica e Riab Amb. Scoliosi e disfunzioni temporo ma | 9316 | MOBILIZZAZIONE DI ALTRE ARTICOLAZIONI | 10 | 23 | 15 | 18 | 6 |
| 563110 | Med Fisica e Riabilitazione Amb. Divisionale | 9326 | RISOLUZIONE MANUALE DI ADERENZE ARTICOLARI | 13 | 1 | 6 | 5 | |
| 563110 | Med Fisica e Riabilitazione Amb. Divisionale | 93054 | TEST POSTUROGRAFICO | | | 1 | | |
| 563110 | Med Fisica e Riabilitazione Amb. Divisionale | 93564 | BENDAGGIO ADESIVO ELASTICO | | | | | 3 |
| 563110 | Med Fisica e Riabilitazione Amb. Divisionale | 98591 | TERAPIA AD ONDE D?URTO FOCALIZZATE PER PATOLO | 21 | 29 | 9 | 26 | 35 |
| 563110 | Med Fisica e Riabilitazione Amb. Divisionale | 99297 | MESOTERAPIA (inclusa antalgica) | 34 | 24 | 6 | 15 | 6 |
| 563110 | Med Fisica e Riabilitazione Amb. Divisionale | 99299 | INIEZIONE DI TOSSINA BOTULINICA | 20 | 13 | 16 | 18 | |
| 563110 | Med Fisica e Riabilitazione Amb. Divisionale | 99991 | LASER TERAPIA ANTALGICA | 37 | 40 | 31 | | |
| 563114 | Med Fisica e Riab Amb. Scoliosi e disfunzioni temporo ma | 897B2 | PRIMA VISITA DI MEDICINA FISICA E RIABILITAZIONE | 120 | 112 | 121 | 139 | 86 |

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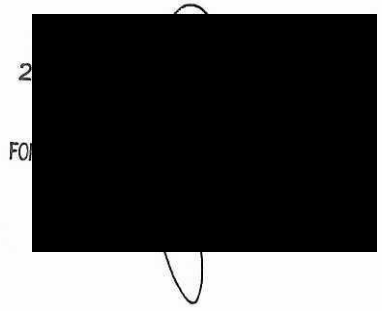
FONDAZIONE IRCCS POLICLINICO SAN MATTEO - PAVIA - DIREZIONE MEDICA DI PRESIDIO

# ATTIVITA' AMBULATORIALI 2013-2017

| CDC_EROG | ATTIVITA' AMBULATORIALI | PREST | DESCR_BREVE | 2013 | 2014 | 2015 | 2016 | 2017 |
|---|---|---|---|---|---|---|---|---|
| 563110 | Med Fisica e Riab Amb. Divisionale | 897 | PRIMA VISITA | 386 | 379 | 373 | 421 | 398 |
| 563114 | Med Fisica e Riab Amb. Scoliosi e disfunzioni temporo ma | 897 | PRIMA VISITA | 60 | 37 | 60 | 72 | 131 |
| 563110 | Med Fisica e Riab Amb. Divisionale | 8192 | INIEZIONE DI SOSTANZE TERAPEUTICHE NELL'ARTICOL | 21 | 17 | 12 | 4 | 28 |
| 563110 | Med Fisica e Riab Amb. Divisionale | 8901 | VISITA DI CONTROLLO | 569 | 571 | 549 | 579 | 586 |
| 563114 | Med Fisica e Riab Amb. Scoliosi e disfunzioni temporo ma | 8901 | VISITA DI CONTROLLO | 298 | 349 | 409 | 405 | 538 |
| 563110 | Med Fisica e Riabilitazione Amb. Divisionale | 8907 | VISITA MULTIDISCIPLINARE | | 1 | | | |
| 563110 | Med Fisica e Riabilitazione Amb. Divisionale | 9303 | VALUTAZIONE PROTESICA | | | 2 | 2 | 1 |
| 563114 | Med Fisica e Riab Amb. Scoliosi e disfunzioni temporo ma | 9303 | VALUTAZIONE PROTESICA | 43 | 61 | 58 | 67 | 40 |
| 563110 | Med Fisica e Riabilitazione Amb. Divisionale | 9315 | MOBILIZZAZIONE DELLA COLONNA VERTEBRALE | 16 | 15 | 18 | 27 | 14 |
| 563114 | Med Fisica e Riab Amb. Scoliosi e disfunzioni temporo ma | 9315 | MOBILIZZAZIONE DELLA COLONNA VERTEBRALE | | | | 3 | 12 |
| 563114 | Med Fisica e Riab Amb. Scoliosi e disfunzioni temporo ma | 9316 | MOBILIZZAZIONE DI ALTRE ARTICOLAZIONI | 10 | 23 | 15 | 18 | 6 |
| 563110 | Med Fisica e Riabilitazione Amb. Divisionale | 9326 | RISOLUZIONE MANUALE DI ADERENZE ARTICOLARI | 13 | 1 | 6 | 5 | |
| 563110 | Med Fisica e Riabilitazione Amb. Divisionale | 93054 | TEST POSTUROGRAFICO | | | 1 | | |
| 563110 | Med Fisica e Riabilitazione Amb. Divisionale | 93564 | BENDAGGIO ADESIVO ELASTICO | | | | | 3 |
| 563110 | Med Fisica e Riabilitazione Amb. Divisionale | 98591 | TERAPIA AD ONDE D?URTO FOCALIZZATE PER PATOLO | 21 | 29 | 9 | 26 | 35 |
| 563110 | Med Fisica e Riabilitazione Amb. Divisionale | 99297 | MESOTERAPIA (inclusa antalgica) | 34 | 24 | 6 | 15 | 6 |
| 563110 | Med Fisica e Riabilitazione Amb. Divisionale | 99299 | INIEZIONE DI TOSSINA BOTULINICA | 20 | 13 | 16 | 18 | |
| 563110 | Med Fisica e Riabilitazione Amb. Divisionale | 99991 | LASER TERAPIA ANTALGICA | 37 | 40 | 31 | | |
| 563114 | Med Fisica e Riab Amb. Scoliosi e disfunzioni temporo ma | 897B2 | PRIMA VISITA DI MEDICINA FISICA E RIABILITAZIONE | 120 | 112 | 121 | 139 | 86 |



# ATTIVITA' AMBULATORIALI 2018-2022

| CDC_EROG | ATTIVITA' AMBULATORIALE | PREST | PRESTAZIONI | 2018 | 2019 | 2020 | 2021 | 2022 |
|---|---|---|---|---|---|---|---|---|
| 563110 | Med Fisica e Riab. Amb. Divisionale | 8192 | INIEZIONE DI SOSTANZE TERAPEUTICHE | 34 | 40 | 18 | 5 | 13 |
| 563114 | Med Fisica e Riab. Amb. Scoliosi e disfunzioni temporo m | 8901 | VISITA DI CONTROLLO | 358 | 363 | 210 | 189 | 255 |
| 563110 | Med Fisica e Riab Amb. Divisionale | 8907 | VISITA MULTIDISCIPLINARE | | | | | 1 |
| 563110 | Med Fisica e Riab Amb. Divisionale | 89442 | TEST DEL CAMMINO | | | 1 | | |
| 563114 | Med Fisica e Riab Amb. Scoliosi e disfunzioni temporo ma | 897B2 | PRIMA VISITA MEDICINA FISICA E RIABILITAZION | 137 | 225 | 118 | 166 | 124 |
| 563110 | Med Fisica e Riab Amb. Divisionale | 9303 | VALUTAZIONE PROTESICA | 3 | 6 | 1 | 4 | 11 |
| 563114 | Med Fisica e Riab Amb. Scoliosi e disfunzioni temporo ma | 9303 | VALUTAZIONE PROTESICA | 34 | 40 | 18 | 5 | 13 |
| 563110 | Med Fisica e Riabilitazione Amb. Divisionale | 93054 | TEST POSTUROGRAFICO | 3 | 4 | | 1 | |
| 563110 | Med Fisica e Riab Amb. Divisionale | 93055 | TEST STABILOMETRICO STATICO DINAMICO | 3 | 69 | 10 | 10 | 34 |
| 563114 | Med Fisica e Riab Amb. Scoliosi e disfunzioni temporo ma | 93055 | TEST STABILOMETRICO STATICO DINAMICO | | 20 | 11 | 2 | |
| 563110 | Med Fisica e Riab Amb. Divisionale | 9315 | MOBILIZZAZIONE COLONNA VERTEBRALE | 20 | 30 | 15 | 6 | 13 |
| 563114 | Med Fisica e Riab Amb. Scoliosi e disfunzioni temporo ma | 9315 | MOBILIZZAZIONE COLONNA VERTEBRALE | | | | 3 | |
| 563110 | Med Fisica e Riabe Amb. Divisionale | 9316 | MOBILIZZAZIONE DI ALTRE ARTICOLAZIONI | 2 | 5 | | | 3 |
| 563114 | Med Fisica e Riab Amb. Scoliosi e disfunzioni temporo ma | 9316 | MOBILIZZAZIONE DI ALTRE ARTICOLAZIONI | | 2 | 9 | | |
| 563110 | Med Fisica e Riabilitazione Amb. Divisionale | 93351 | AGOPUNTURA CON MOXA REVULSIVANTE | | | | 3 | 8 |
| 563110 | Med Fisica e Riabilitazione Amb. Divisionale | 93564 | BENDAGGIO ADESIVO ELASTICO | | | 2 | | 10 |
| 563110 | Med Fisica e Riabilitazione Amb. Divisionale | 98591 | TERAPIA AD ONDE D'URTO FOCALIZZATE | 25 | 21 | 10 | 13 | 18 |
| 563114 | Med Fisica e Riab Amb. Scoliosi e disfunzioni temporo ma | 98591 | TERAPIA AD ONDE D'URTO FOCALIZZATE | | 3 | | | |
| 563110 | Med Fisica e Riabilitazione Amb. Divisionale | 99297 | MESOTERAPIA (inclusa antalgica) | 13 | 21 | 6 | 5 | 22 |
| 563114 | Med Fisica e Riab Amb. Scoliosi e disfunzioni temporo ma | 99991 | LASER TERAPIA ANTALGICA | 30 | 42 | 23 | 40 | 26 |

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# VISITE FISIATRICHE DI CONSULENZA REPARTI parte A

| DESCRIZIONE | CONSULENZE REPARTI | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 |
|---|---|---|---|---|---|---|---|---|---|
| VISITA DI FISIAT | MED.1 M.I.O.M. REP.11 | 3 | 2 | 4 | 2 | 2 | 1 | | |
| VISITA DI FISIAT | MED.2 M.V. REP.19/19 BIS | 9 | 15 | 16 | 43 | 50 | 38 | 10 | |
| VISITA DI FISIAT | MED.3 REP.15 ex 14 DEG.ZA | | | 1 | | 1 | 2 | 2 | |
| VISITA DI FISIAT | Medicina Generale 1 | | | 1 | | | 1 | | |
| VISITA DI FISIAT | Medicina Generale 2 | | | | | 2 | 1 | | |
| VISITA DI FISIAT | Medicina Gen. Media Intensita | | | | 2 | 2 | | | |
| VISITA DI FISIAT | Medicina Vascolare | 28 | 33 | 24 | 22 | 28 | 18 | 16 | |
| VISITA DI FISIAT | NEFROLOGIA DEGENTI | | | | | 1 | 1 | | |
| VISITA DI FISIAT | NEUROCHIRURGIA DEGENTI | 12 | 17 | 12 | 15 | 15 | 14 | 8 | |
| VISITA DI FISIAT | OCULISTICA DEGENTI | | | | 1 | | | | |
| VISITA DI FISIAT | ONCOEMAT. PED. DEGENTI | 2 | 4 | 1 | 2 | 3 | 1 | | |
| VISITA DI FISIAT | Oncologia Degenti | | | 1 | | | | | |
| VISITA DI FISIAT | Ortopedia Degenti | | 170 | 341 | 407 | 331 | 251 | 19 | |
| VISITA DI FISIAT | Ortopedia degenti Lib Prof | | | | | | | 1 | |
| VISITA DI FISIAT | ORTOPEDIA REP.3 MASCHI | 375 | 223 | | | | | | |
| VISITA DI FISIAT | Ortopedia Week Surgery | 416 | 509 | 600 | 571 | 492 | 511 | 51 | 28 |
| VISITA DI FISIAT | OTORINOLARING. DEGENTI | 2 | 4 | 2 | 3 | 3 | 1 | | |
| VISITA DI FISIAT | PEDIATRIA DEGENTI (3 PIANO) | 6 | 8 | 6 | 4 | 5 | 3 | 1 | 1 |
| VISITA DI FISIAT | PEDIATRIA MAC | | | | | | 1 | | |
| VISITA DI FISIAT | Prericovero - Pediatria Univ. | | | | | 3 | | | |
| VISITA DI FISIAT | PSICHIATRIA DEGENTI | 1 | | | 1 | | | | |
| VISITA DI FISIAT | REUMATOLOGIA DEGENTI | | | | | 1 | 2 | | |
| VISITA DI FISIAT | RIANIMAZIONE I DEGENTI | | 2 | | 3 | 3 | | | |
| VISITA DI FISIAT | RIANIMAZIONE II DEGENTI | | 2 | | 6 | 1 | | | |
| VISITA DI FISIAT | Senologia Degenza | | | | | | 1 | | |
| VISITA DI FISIAT | Traumatologia | | 342 | 456 | 425 | 333 | 427 | 45 | 35 |
| VISITA DI FISIAT | TRAUMATOLOGIA DEGENTI | 317 | 236 | | | | | | |
| VISITA DI RIABIL | MED.2 M.V. REP.19/19 BIS | 3 | 1 | 4 | 6 | 3 | 2 | | |

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# VISITE FISIATRICHE CONSULENZA REPARTI parte B

| DESCRIZIONE | CONSULENZE REPARTI | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 |
|---|---|---|---|---|---|---|---|---|---|
| VISITA DI FISIAT | Rianimazione II Cardiopolmonare | | 13 | 8 | 9 | 4 | 3 | | |
| VISITA DI FISIAT | Attivita di Cure Subacute - Pavia | | 15 | 12 | 16 | 10 | 7 | 6 | 4 |
| VISITA DI FISIAT | BELGIOIOSO REP.B DEGENTI | 1 | 2 | 5 | 7 | 4 | 4 | 2 | |
| VISITA DI FISIAT | CARD. CURE INT. CORONARICHE | | | | | 1 | | | |
| VISITA DI FISIAT | CARDIOCHIR. DEGENTI | | 2 | 1 | 10 | 2 | 7 | | |
| VISITA DI FISIAT | CARDIOLOGIA DEGENZA | 5 | 3 | 5 | 6 | 4 | 1 | | |
| VISITA DI FISIAT | CHIR. VASCOLARE DEGENTI | 6 | 8 | 3 | 14 | 9 | 12 | 4 | |
| VISITA DI FISIAT | Chirurgia Generale 1 Degenti A | 14 | 12 | 3 | 5 | 4 | 2 | | |
| VISITA DI FISIAT | Chirurgia Generale 1 Degenti B | 2 | 3 | 5 | 2 | 2 | 2 | 1 | |
| VISITA DI FISIAT | Chirurgia Generale 2 Degenti C | 3 | 4 | 5 | 4 | 3 | 2 | | |
| VISITA DI FISIAT | Chirurgia Generale 2 Degenti D | 5 | 1 | 3 | 12 | 3 | 2 | 1 | |
| VISITA DI FISIAT | Chirurgia Toracica Degenti | | 2 | 1 | 1 | 2 | 4 | | |
| VISITA DI FISIAT | Cure Palliative Degenti Belg. | 5 | 20 | 11 | 11 | 10 | 8 | | |
| VISITA DI FISIAT | EMATOLOGIA DEGENTI | 4 | 3 | 5 | 5 | 6 | 2 | | |
| VISITA DI FISIAT | Ginecologia Degenti (sez.22) | | | 1 | | 1 | 1 | | |
| VISITA DI FISIAT | INTRA MOENIA DEGENTI | 12 | 3 | 5 | 16 | 8 | 1 | | |
| VISITA DI FISIAT | MAL. INF.TROPICALI DEGENTI | 1 | | | | | | 1 | |
| VISITA DI FISIAT | MAL. INFETTIVE DEGENTI | 4 | 3 | 5 | 7 | 3 | | | |
| VISITA DI FISIAT | MALAT. APP. RESP - DEGENTI 3 | 1 | 1 | | 2 | | | | |
| VISITA DI FISIAT | MALAT. APP. RESPIRAT. DEGENTI 1 | 2 | 3 | 2 | 6 | 2 | | | |
| VISITA DI FISIAT | MALAT. APP. RESPIRAT. DEGENTI 2 | 2 | 3 | 2 | 3 | 2 | | | |
| VISITA DI FISIAT | MALAT. APP. RESPIRAT. TRAPIANTI | 2 | | | 1 | 4 | | | |
| VISITA DI FISIAT | Maxillo Facciale c/o ORL | 1 | 1 | 3 | 4 | 1 | | | |

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Online version at http://www.minervamedica.it

European Journal of Physical and Rehabilitation Medicine 2016 June;52(3):379-88

ORIGINAL ARTICLE

# Rehabilitation and functional recovery after masseteric-facial nerve anastomosis

Chiara PAVESE [1], Miriam CECINI [1], Alessandro LOZZA [2], Federico BIGLIOLI [3]
Claudio LISI [4], Maurizio BEJOR [1, 5], Elena DALLA TOFFOLA [1, 4] *

[1]Department of Clinical, Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Pavia, Italy; [2]Mondino National Institute of Neurology Foundation, IRCCS, Pavia, Italy; [3]Department of Maxillo-Facial Surgery University of Milan San Paolo Hospital, Milan, Italy; [4]Rehabilitation Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [5]Don Carlo Gnocchi ONLUS Foundation, Milan, Italy

*Corresponding author: Elena Dalla Toffola, Rehabilitation Unit, Fondazione IRCCS Policlinico San Matteo, Viale Golgi 19, 27100 Pavia, Italy.
E-mail: elena.dallatoffola@unipv.it

## ABSTRACT

BACKGROUND**:** After masseteric-facial nerve (V-VII) anastomosis, a new neurological circuit oversees the facial muscles and patients should learn to activate the facial movements using the masseteric function.
AIM**:** To monitor the rehabilitative protocol of facial muscles activation through teeth clenching and to assess the clinical evolution after V-VII anastomosis in terms of facial symmetry and functional recovery.
DESIGN**:** Case series.
SETTING**:** Outpatients clinic.
POPULATION**:** Eleven patients undergone V-VII anastomosis for complete unilateral facial palsy.
METHODS**:** After surgery, patients underwent a needle electromyography (EMG) and a rehabilitative training with mirror feedback to learn how to reach the symmetry at rest and during facial movements through teeth clenching. The rehabilitative protocol at the first clinical evaluation has been monitored through the Italian version of Sunnybrook Facial Grading System (SFGS) and the Software Facial Assessment by Computer Evaluation (FACE). Functional limitations and quality of life have been evaluated using the Italian version of Facial Disability Index (FDI). The clinical evolution at 18 months was evaluated with EMG, SFGS, biting evaluation and FDI.
RESULTS**:** At the first clinical evaluation after reinnervation, through teeth clenching patients displayed an improvement of symmetry at rest, symmetry of voluntary movement, symmetry of smile and composite score of SFGS. Objective measurement of facial structures with FACE system demonstrated an improvement of symmetry at rest and during smile through teeth clenching. At 18 months patients displayed a good reinnervation with a further improvement of SFGS scores and reduction of functional disability. No biting deficit has been observed.
CONCLUSION**:** After V-VII anastomosis, at the first rehabilitative visit, patients learn to activate the reinnervated facial muscles through teeth clenching. Eighteen months after the anastomosis, patients display a further improvement of voluntary control on facial symmetry and smile and a reduction of disability.
CLINICAL REHABILITATION IMPACT: Our study illustrates the rehabilitative protocol after V-VII anastomosis and analyzes the clinical evolution after this intervention in terms of recovery of facial symmetry and reduction of disability. This will be instrumental to standardize the rehabilitative protocol among different centers and to choose the best patient-tailored surgical approach for subjects affected by complete facial palsy.

(*Cite this article as*: Pavese C, Cecini M, Lozza A, Biglioli F, Lisi C, Bejor M *et al.* Rehabilitation and functional recovery after masseteric-facial nerve anastomosis. Eur J Phys Rehabil Med 2016;52:379-88)

**Key words:** Facial nerve - Facial paralysis - Physical Therapy Modalities - Biofeedback, Psychology - Masseteric nerve.

Patients affected by complete facial palsy in which a spontaneous recovery is not expected, are eligible for a surgical intervention to restore facial motility.[1] This group includes subjects whose facial nerve has been cut off during surgical procedures (*i.e.* maxillofacial interventions or acoustic neuroma excisions)

or traumatic accidents, as well as patients affected by other forms of facial palsy, who have not been recovering over the expected time.[2]

In cases in which the nerve is transected, the prompt restoration of anatomical continuity through suture is recommended.[3] When this procedure is not possible, numerous other surgical options are available.[3] In order to select the best patient-tailored intervention, many factors are to be considered, including age, etiology of palsy, time elapsed since injury, and general health status.[1] Moreover the neurophysiological assessment plays a key role in decision guidance: when facial muscles show vitality, proved by signs of fibrillation at the needle electromyography (EMG), an appropriate donor nerve can be anastomized to the distal part of VII nerve to re-establish facial muscles' innervation.[4]

For early reanimation, in 2012 Biglioli *et al*. used the anastomosis of the masseteric nerve to the entire facial nerve trunk with a great auricular nerve interpositional graft.[5] This intervention showed satisfying results in terms of quality of reinnervation and recovery of facial symmetry.[5, 6]

This anastomosis establishes a new neurological circuit: the facial muscles are reinnervated by the masseteric nerve and their contraction is determined through teeth clenching. Patients are afterwards commonly addressed to a rehabilitation program to learn how to produce the facial movements through a teeth clenching trigger. In literature rehabilitation after Bell's palsy has already been investigated, [7] but no consensus guidelines for the rehabilitative protocol after V-VII anastomosis are available.[5, 8]

Primary objective of the study is to describe and monitor our protocol of facial muscles activation through teeth clenching during the first rehabilitation session after reinnervation with masseteric nerve. Secondary aim is to follow-up for 18 months the clinical evolution in terms of facial symmetry and functional recovery.

## Materials and methods

### *Patients*

The study evaluates 11 patients affected by unilateral complete facial palsy undergone V-VII anastomosis followed by a rehabilitative program at our Rehabilitation Unit at IRCCS San Matteo University Hospital Foundation, Pavia, Italy. The mean age was 42.7 (±15) years, 6 (54.5%) were males. The etiology of facial palsy was postsurgical in 9 patients (6 after acoustic neuroma excision, 1 after astrocytoma, 2 after skull base tumor), post-traumatic (skull base fracture) in 1 and idiopathic in 1. The side of palsy was right in 6 cases (54.5%). Table I summarizes the baseline characteristics of patients.

Clinical evaluations and interventions at each time point are reported in Figure 1.

All patients underwent EMG examination before surgery. The areas examined were the paralyzed muscles of the face innervated by the facial nerve and by the motor component of the ipsilateral trigeminal nerve (masseter and temporal).

All patients showed signs of electrical involuntary activity (fibrillations, positive sharp waves) in the muscles physiologically innervated by the facial nerve, due to complete denervation; this activity was compatible with a maintained electrical properties of the muscle adapted to receive reinnervation.

The masseter and temporal muscle EMG have been

TABLE I.—*Baseline characteristics of patients.*

| Patient | Age | Sex | Side | Etiology | Palsy-V-VII (Months) | V-VII – Rehabilitation (Months) |
|---|---|---|---|---|---|---|
| 1 | 38 | Female | Right | Surgery | 19 | 4 |
| 2 | 34 | Male | Right | Surgery | 18 | 4 |
| 3 | 61 | Male | Right | Surgery | 7 | 15 |
| 4 | 29 | Male | Left | Idiopatic | 19 | 11 |
| 5 | 31 | Female | Right | Surgery | 13 | 7 |
| 6 | 53 | Male | Right | Surgery | 14 | 12 |
| 7 | 45 | Female | Left | Surgery | 8 | 6 |
| 8 | 45 | Female | Left | Surgery | 11 | 3 |
| 9 | 17 | Male | Right | Trauma | 9 | 6 |
| 10 | 48 | Male | Right | Surgery | 25 | 6 |
| 11 | 58 | Female | Left | Surgery | 16 | 9 |

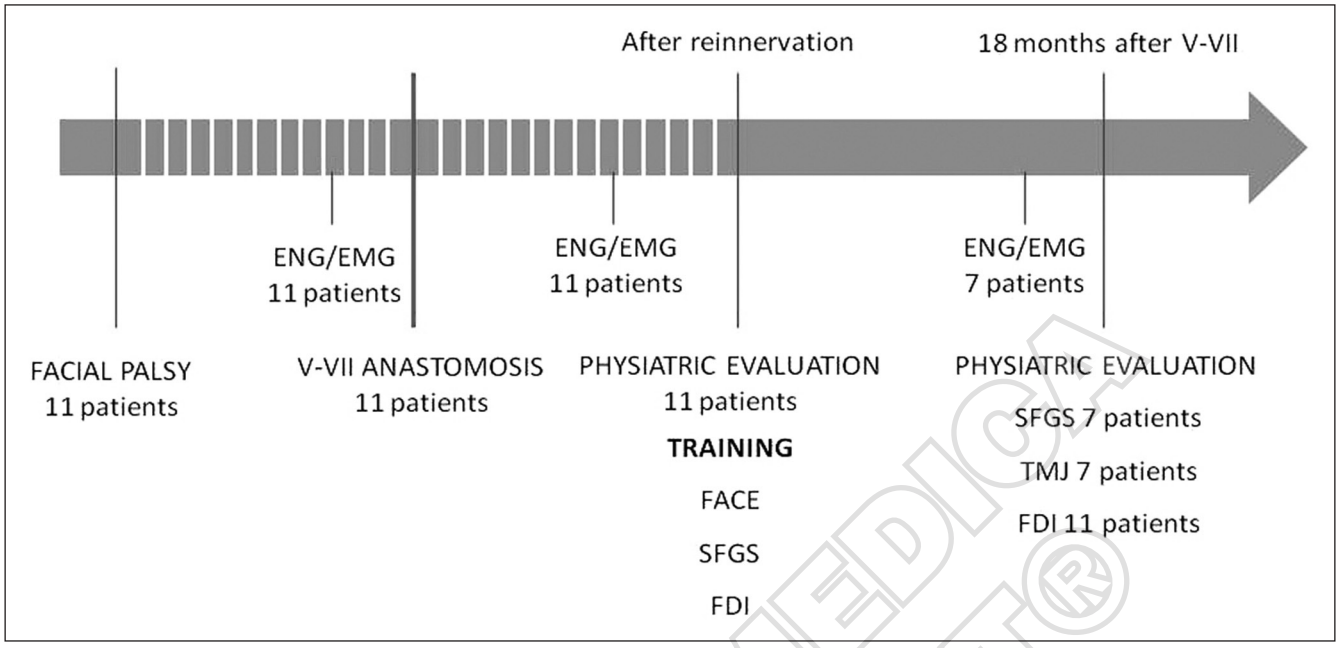


Figure 1.—Flow-chart of the assessments performed in each time point. V-VII anastomosis: masseteric-facial nerve anastomosis. SFGS: Sunnybrook Facial Grading System. FACE: Facial Assessment by Computer Evaluation (FACE) Software. FDI: Facial disability Index; TMJ: temporomandibular joint evaluation.

done to assess the integrity of the donor trigeminal nerve (masseteric nerve) and showed normal activity and EMG pattern.

All patients underwent a V-VII anastomosis with an interpositional graft of the great auricular nerve, according to the technique described by Biglioli *et al*.[5] The anastomosis was performed at a mean of 14,5 (±5.5) months after the onset of palsy. Patients were addressed to the physiatric evaluations by surgeons after the beginning of reinnervation.

All the procedures conformed to the standards established by the Declaration of Helsinki and were approved by our Ethical Committee and all patients gave their written informed consent to the collection and use for research purpose of their clinical data and photographs, according to our Institutional Review Board requirement.

### *Clinical evaluation after surgery*

After the anastomosis, patients underwent a neurophysiological assessment and a physiatric evaluation after the beginning of reinnervation.

During the first physiatric evaluation with signs of reinnervation, on average 7.5 (±3.8) months after the anastomosis, the facial symmetry was assessed using the Italian version of Sunnybrook Facial Grading System without and with the teeth clenching.[9, 10] The objective measurement of symmetry at rest and during smile, without and with the teeth clenching, was performed using the Facial Assessment by Computer Evaluation (FACE) Software.[11, 12] Functional and social/well-being limitations were evaluated using the Italian version of Facial Disability Index.[13, 14]

### *Rehabilitative treatment*

At the first visit all patients underwent a rehabilitative training. As a consequence of the V-VII anastomosis a new brain circuit is established, in which the facial muscles of the affected side are put under the control of the ipsilateral masseteric nerve. Therefore we established a novel rehabilitation protocol aimed at instructing patients to control facial movements clenching their teeth. To this aim we have adapted the protocol currently in use at our Centre for rehabilitation after hypoglossal-facial nerve anastomosis in which facial muscles are controlled by tongue movements.[15]

The goals of the rehabilitative program are: 1) to make the patient conscious of the newly-formed motor circuit; 2) to adapt the strength of teeth clenching in order to produce the most symmetric movements; 3) to reach automatism in facial control.

Before the onset of signs of reinnervation, patients were educated to perform only a slight facial massage. At the beginning of reinnervation, patients were instructed to execute facial exercises, and were motivated to repeat them daily at home. The exercises consisted in activation of facial muscles, mediated by teeth clenching with a visual mirror-based feedback control. Patients were initially instructed to reach the symmetric rest position of mouth and to keep it for 5 seconds. With the progression of reinnervation and muscle recruitment, patients were taught to smile with closed lip and at a later stage with open mouth, progressively modulating the strength of teeth clenching to optimize the symmetry of the expression. The last step consisted in the activation of the mimic muscles starting from the open mouth position. The rehabilitative program was updated at each clinical control.

### *Follow-up evaluation at 18 months*

The clinical evolution at 18 months was evaluated through the neurophysiological measurement, the Italian versions of SFGS and FDI and with a specific biting evaluation. Data concerning neurophysiology, symmetry assessment with SFGS and biting evaluation at 18 months were available for seven patients, functional and social/well-being function was evaluated in all patients, in 4 cases over a phone call.

### *Outcome measures*

#### Neurophysiological assessment after surgery

The electromyographic examination was repeated to assess the presence of reinnervation in the facial muscles about five months after the anastomosis.

Patients underwent a further electromyographic examination to evaluate the reinnervation of facial and masseteric muscles at 18 months.

#### Sunnybrook Facial Grading System

The Sunnybrook Facial Grading System grades the facial symmetry at rest, during voluntary movement and the severity of facial synkinesis. The scale provides three subscores: the symmetry at rest score ranges from -20 to 0 (with 0 indicating complete symmetry at rest), the symmetry of voluntary movement score ranges from 20 to 100 (with 100 indicating maximum symmetry of movement) and the synkynesis score ranges from 0 (absence of synkynesis) to 15 (severe widespread synkynesis). By integrating the three subscores, a composite score is obtained, which ranges from 0, for complete facial palsy, to 100, indicating normal facial function.[9, 10] Furthermore, we report the single data of SFGS referring to lower face: cheek symmetry at rest (range -2 – 0), mouth symmetry at rest (range -1 – 0), symmetry of open mouth smile (range 1-5) with and without teeth clenching.

#### Software-based assessment of facial symmetry FACE

The degree of symmetry in resting position and during smile, with and without teeth clenching, was measured using the Facial Assessment by Computer Evaluation (FACE) Software.[11] This is an objective biometric system, which provides quantitative data regarding resting position and dynamic excursion of key facial structures from standard patient photographs.

At each clinical assessment, patients were photographed in resting position and while smiling using an Exilim High-Speed EX-F1 camera (Casio, Tokyo, Japan) on a tripod at a distance of 60 cm from the subject's face, straight on, at a resolution of 6 megapixels. All photographs were taken, processed and analyzed by the same physician with expertise with the FACE software.[12]

We report the measures of symmetry without and with teeth clenching activation: at rest we measured the corner deviation and lower and upper lip deviation between healthy and affected side in millimeters; during voluntary smile we measured the degree of lip excursion both in healthy and in affected side in degrees.

#### Facial Disability Index

Functional and social/well-being limitations related to facial palsy were subjectively evaluated using the Italian version of Facial Disability Index.[13] This is a 10-item questionnaire, which is composed by two sub-

scales: the physical function subscale evaluates difficulty in eating, drinking, speech, eye lacrimation and oral hygiene. The social function subscale examines individual calmness, social integration, social interaction, sleep quality and social participation. Every item is rated on a six point-scale, ranging from severe functional and social disability to absence of disability. Both the subscales generate a score, with 100 meaning complete physical or social/well-being function.[13, 14]

### Biting evaluation

Due to the limited follow-up of patients treated with this recently established surgical technique and the consequent lack of data concerning the clinical evolution and possible side effects of V-VII anastomosis, we investigated the presence of biting disorders due to complete transection of the masseter branch of V cranial nerve and subsequent denervation of masseter muscle. On inspection, we evaluated the presence of local swelling, deformation, deviation of the jaw and teeth wear. The joint was palpated during active opening and closing, during active deviation to the left and right, and jaw protrusion, to evaluate if palpationelicited pain. The masticatory muscles (masseter, temporal and medial pterygoid) have been palpated to discover local pain and areas of tenderness.

Through the functional examination we evaluated the range of movement (normal values: active opening 42-55 mm, active deviation of the mandible to the left and right 10-15 mm, active forward protrusion of the jaw 0-10 mm), the line of the vertical jaw opening (straight or deviating, smooth or jerky) and the presence of joint clicking or grating sounds during all active movements.[16]

### *Statistical analysis*

Data were described as mean and standard deviation or median and interquartile range if continuous and as counts and percentage if categorical. The comparison between groups was performed using t test and Wilcoxon signed rank test, as appropriate. A 2-sided P-value<0.05 was considered to be statistically significant. GraphPad Prism 5 was used for computation.

## Results

### *Neurophysiological assessments*

After surgery, signs of initial reinnervation of facial muscles were observed 5-6 months after the anastomosis.

At the end of the follow-up all patients showed signs of reinnervation with discrete voluntary activity recorded in the risorius muscle (needle recording) and obtained by masticatory activity (clenching the teeth). Moreover EMG activity showed partial recovery of voluntary activity also in the denervated masseter muscle, maybe due to collateral motor branches.

### *Monitoring of the rehabilitative treatment*

At the first clinical evaluation at our Rehabilitation Unit, patients showed signs of reinnervation of the face muscles, but were not able to use this resources. Patients were trained with the rehabilitative exercise, *i.e.* voluntary activation of the facial muscles mediated by teeth clenching. Table II shows the improvement of facial symmetry during the rehabilitative training, as assessed by the SFGS (Wilcoxon Signed-Rank Test).

Table II.—*Sunnybrook Facial Grading System scores, median (interquartile range) and P-value without (w/o) and with teeth clenching at the first clinical evaluation after reinnervation and 18 months after the anastomosis.*

| | First physiatric visit (N.=11) | | | Eighteen months after V-VII (N.=7) | | |
|---|---|---|---|---|---|---|
| | W/o teeth clenching | With teeth clenching | P-value | W/o teeth clenching | With teeth clenching | P-value |
| Composite Score | 16 (8-18) | 39 (26 – 49) | 0.0038 | 16 (9-25) | 54 (46-59) | 0.0156 |
| Symmetry at rest | -20 (-20 – -15) | -10 (-10 – -5) | 0.0048 | -15 (-20 – -10) | -5 (-10 – -5) | 0.0568 |
| – Cheek symmetry | -2 (-2 – -2) | -1 (-1-0) | 0.0048 | -2 (-2 – -1) | -1 (-1-0) | 0.1736 |
| – Mouth symmetry | -1 (-1 – -1) | 0 (-1-0) | 0.006 | -1 (-1-0) | 0 (0-0) | 0.0719 |
| Symmetry of movement | 28 (28-36) | 44 (40-56) | 0.0038 | 32 (28-40) | 44 (40-56) | 0.0213 |
| – Open mouth smile | 1 (1-1) | 2 (2-3) | 0.0032 | 1 (1-1) | 3 (3-4) | 0.0335 |
| Synkinesis | 0 (0-0) | 0 (0-2) | 0.0975 | 0 (0-0) | 0 (0-4) | 0.1736 |

TABLE III.—*Objective measurement of facial structures with FACE system, at rest and during smile, before and during the biting activation at the first visit after surgery, mean (standard deviation).*

| | W/o teeth clenching | With teeth clenching | P-value |
|---|---|---|---|
| Symmetry at rest | | | |
| – Lip corner deviation (mm) | 7.68 (2.20) | 2.77 (2.47) | <0.001 |
| – Lower lip deviation (mm) | 4.52 (1.64) | 1.65 (1.64) | 0.0029 |
| – Upper lip deviation (mm) | 3.65 (1.89) | 1.18 (1.22) | 0.0074 |
| Symmetry during smile | | | |
| – Δ (healthy-affected) lip corner angle (degrees) | 16.7 (10.26) | 6.16 (7.11) | <0.001 |

Through teeth clenching, a significant improvement was observed in all considered parameters (symmetry of face and mouth at rest, symmetry of voluntary movement and smile and composite score), except facial synkinesis. Facial synkinesis were absent without teeth clenching and did not significantly improve during teeth clenching.

Table III shows the objective improvement of facial symmetry during the masseteric activation, as measured using the FACE system (paired *t*-test) (Figure 2). Through the voluntary activation of facial muscles clenching their teeth, patients improved the facial symmetry in rest position and during smile. At rest, during teeth clenching activation, a significant reduction of asymmetry of lip corner deviation, upper and lower lip deviation was observed. During voluntary smile, the difference between lip corner of healthy side compared to affected side displayed a substantial reduction through teeth clenching.

Figure 3 shows the subjective evaluation of facial palsy-related physical and social/well-being functions as assessed by the Facial Disability Index.

At the first clinical evaluation patients displayed substantial disability, with limitations in individual well-being and social participation. The median physical function subscore was 55/100 and the social/well-being subscore was 60/100.

### *Follow-up evaluation at 18 months*

Eighteen months after the anastomosis, through teeth clenching patients showed a significant improvement of SFGS score of symmetry during voluntary movement and smile and composite score, as reported in Table II.

Symmetry of voluntary movement and composite score of SFGS with teeth clenching display a significant improvement at 18 months in comparison with the first physiatric assessment (P=0.04 and 0.02, respectively, Wilcoxon signed-rank test, analysis included only the 7 patients with 18-month follow-up).

All patients referred that symmetry at rest and during voluntary facial movement was mediated by the automatic activation of face muscles, due to the light contact of teeth, without clenching.

Three patients showed mild ocular synkinesis during mouth movements (*i.e.* snarling, smiling and lip puckering).

At the biting evaluation no patients displayed symptoms or signs of temporomandibular joint dysfunction with deficits of mastication.

The subjective evaluation with Facial Disability Index questionnaire 18 months after the anastomosis showed a significant improvement of physical function (P-value 0.0038) and a trend of improvement in social/well-being function (P-value 0.066) (Figure 3). The median physical function subscore was 70/100 and the social/well-being subscore was 76/100.

## Discussion

Our study demonstrates that at the first rehabilitative visit after V-VII anastomosis patients learn to activate the reinnervated facial muscles through teeth clenching and eighteen months after the anastomosis, patients display a further improvement of voluntary control on facial symmetry and smile and a reduction of disability.

Our data demonstrate the importance of teaching to the patients the correct technique to activate the reinnervated facial muscles after V-VII anastomosis. Indeed we verified that they are not able to learn that without a specific training. The facial motility is gradually recovered, first of all with voluntary and energetic triggering of biting. At a later stage, after completion of reinnervation and regular training, slightly clenching the teeth was enough to activate the reinnervated muscles. Therefore the evaluation of muscles activation without teeth

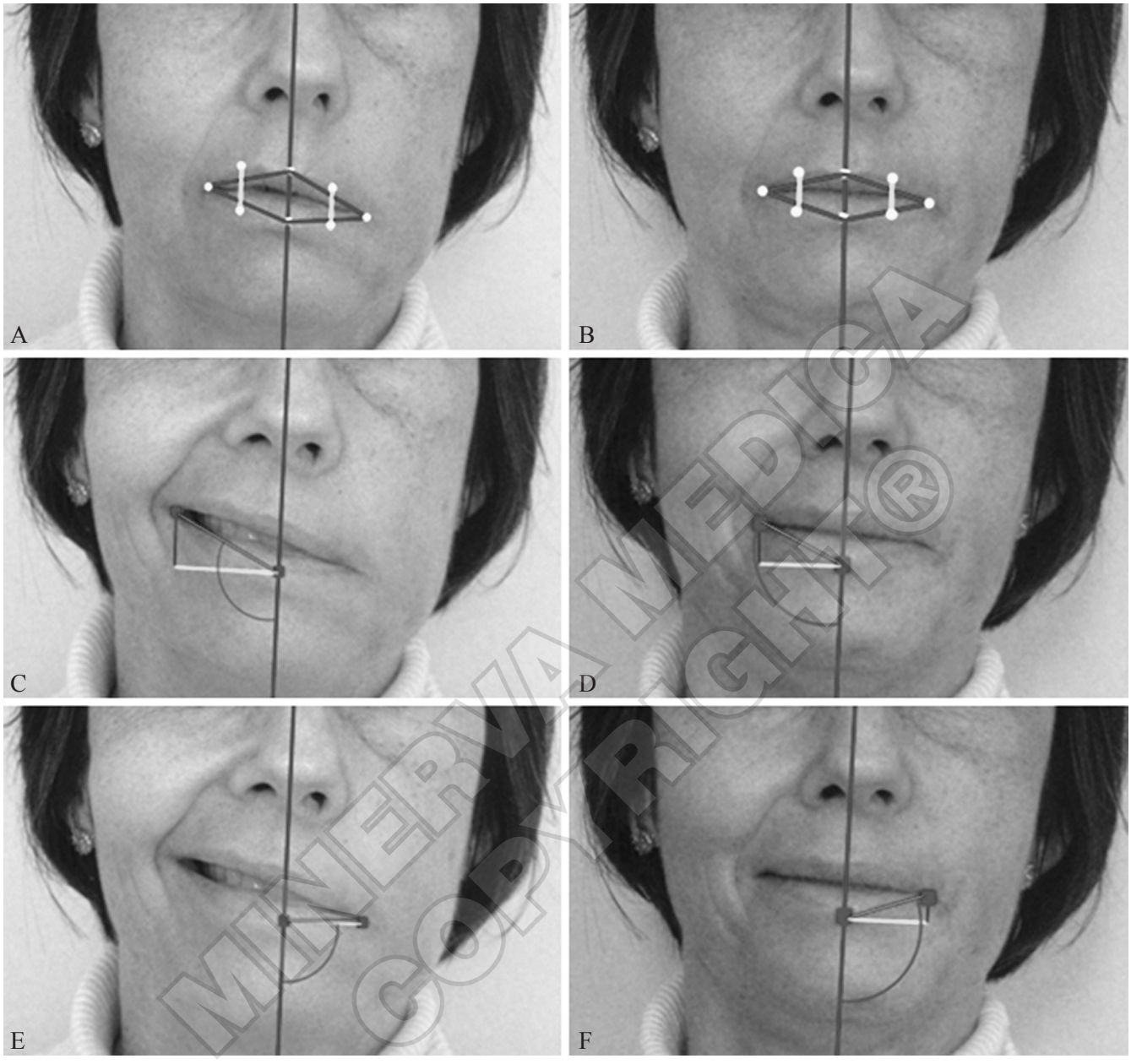


Figure 2.—Objective measurement of facial structures with FACE system. Patient affected by left facial palsy, at the first physiatric visit after V-VII anastomosis. Upper panels: symmetry at rest before (A) and during (B) the biting activation; measurement of corner deviation and lower and upper lip deviation between the two sides. Middle panel: degree of lip excursion of the healthy side during voluntary smile before (C) and during (D) the teeth clenching. Lower panel: degree of lip excursion of the affected side during voluntary smile before (E) and during (F) the teeth clenching. FACE: Facial Assessment by Computer Evaluation (FACE) Software.

clenching was very difficult, especially for symmetry at rest. No patients reported a symmetric smile during a spontaneous laugh.

Finally the patients displaying a major recovery, were able to smile by opening or closing the mouth, as reported by Hontanilla *et al*.[8]

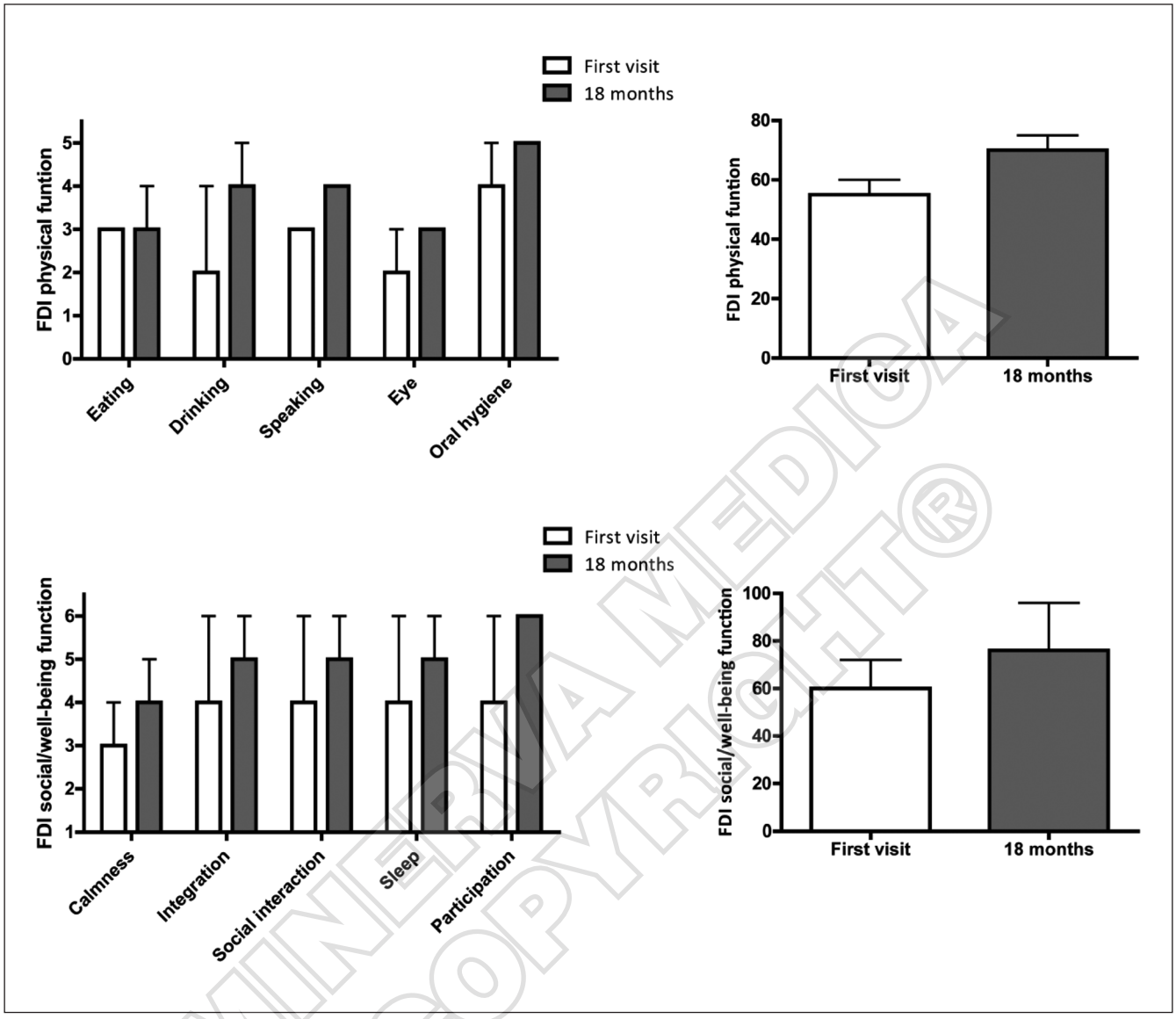


Figure 3.—Physical function and social/well-being function scores (median and interquartile range) evaluated using the Italian version of Facial Disability Index at the first physiatric visit on average six month after surgery (white) and at 18-month follow-up (black). Higher scores indicate better function. FDI: Facial Disability Index.

Since our patients performed their rehabilitation program at home, it was very important to regularly (about every two months) follow-up the progression of recovery and the eventual appearance of ocular synkynesis. A tight control makes the patients conscious of the clinical improvement and of the intensity of teeth clenching required to activate the facial muscles symmetrically and improves the compliance to treatment.

The recovery of spontaneous smile after the anastomosis of facial nerve with a donor nerve is theoretically not expected, since the emotive control of facial expressions depends on extrapyramidal regulation to the facial motor nucleus.[17] In line with this assumption, none of the patients in our study recovered a symmetric spontaneous smile. However, Manktelow *et al*. reported a restoration of spontaneous smile after a microneurov-

ascular muscle transfer innervated by masseter motor nerve and postulate that this phenomenon derives from neural plasticity.[18]

Further studies are necessary to assess whether a reorganization of smiling and teeth clenching cortical areas after reinnervation of facial muscles with the masseteric nerve is possible.[19]

Up to date, many interventions for early facial reanimation are available, but there is no general consensus as to which is the best technique. Randomized controlled clinical trials comparing different surgical approaches are yet to be performed. Therefore, the systematic documentation of the results of each surgical approach with widespread and validated outcome measures is a crucial point to allow the systematic comparison of results among different centres and techniques.[20]

To this aim, we have opted to use three independent and well-established measurement tools to investigate the outcome of V-VII anastomosis in our patient series. To evaluate the recovery of facial symmetry, we chose to employ SFGS, which one of the most employed grading system worldwide, whose usage has been suggested by many Authors.[21-23] As a complementation to the SFGS, we have also employed a computer-assisted system, thereby demonstrating an objective improvement of mouth symmetry at rest and during smiling through the teeth clenching activation. Finally, to assess the impact of V-VII anastomosis and rehabilitation on patients' quality of life, we have also included a patient-reported outcome measure.[24] Overall our study significantly adds on the current literature on the effects of V-VII anastomosis and rehabilitation and should help in comparing different treatment options and guiding the choice of the most suitable approach for patients with severe facial palsy eligible for facial reanimation. Moreover it provides a description of the rehabilitative protocol after V-VII: this will be instrumental to the standardization of treatments among different centres, with positive returns on patients' care and research in the field of facial palsy.

## Conclusions

After V-VII anastomosis, patients with complete facial palsy show a good reinnervation of muscles and no iatrogenic damages. Through a rehabilitative training they learn to activate facial muscles with teeth clenching trigger and they reach a good symmetry of face and smile. Eighteen months after the anastomosis, patients show a further improvement of symmetry and reduction of functional disability.

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# Interobserver reliability of ultrasound assessment of haemophilic arthropathy: radiologist vs. non-radiologist

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Haemophilia is characterized by spontaneous or traumatic, internal or external bleeding into mucous membranes, joints and muscles (subcutaneous haematoma, oral bleeding, epistaxis, haematuria, gastrointestinal and central nervous system bleeding) [1,2].

Joints (particularly the elbow, knee and ankle) and muscles are the main sites of bleeding in patients with haemophilia. Repeated bleeding causes gradual joint deterioration, which starts with inflammation of the synovial membrane and leads on to the development of severe arthritis haemophilic arthropathy (HA). Such degeneration leads to limited function and persistent pain in the affected joints.

Haemophilic arthropathy contributes to the greatest morbidity and cost in the haemophilic population [3]. The management of this condition has been revolutionized by the introduction of prophylactic treatment with clotting factor replacements. Regular monitoring of joint condition is extremely important in order to appropriately assess, manage or take preventive action to reduce or slow down the degenerative process [4].

Diagnostic imaging includes conventional radiology, computerized tomography (CT), ultrasonography (US) and magnetic resonance imaging (MRI).

Although MRI is the most complete and the most sensitive imaging technique for diagnosing musculoskeletal complications associated with haemophilia, it cannot be used routinely as it is not available in all hospitals, costs are high, there can be technical problems (examination times) and children require sedation [4]. Furthermore, a potential shortcoming of MRI is the lack of a reliable and valid correlation between MR images and clinical joint status in real time. In addition, MR images frequently do not correlate with clinical status [5].

In recent years, US examination has been shown to be of value in the diagnosis and control of the evolution of musculoskeletal problems in haemophilia patients [4].

It is a fast, effective, safe, available, comparative, real-time technique that can help confirm clinical examination [4]. It can be performed at the bedside, on a daily basis if necessary, and little or no advance preparation is needed. It is inexpensive, accessible and easy to carry out on children (no sedation required).

Recent studies have reported a correlation between US and MRI measurements in HA, particularly in the detection of joint bleeds, synovial hyperplasia and joint erosions [6].

Ultrasonography has various advantages: it provides objective measurements of echostructure (solid vs. liquid content), lesion size and exact location, vascularization, and muscle or tendon ruptures; it provides high quality images; it is a cheap, quick and harmless technique, for which paediatric patients do not require sedation; US allows the dynamic exploration of muscles and joints, including comparisons with healthy tissues; finally, US can be used as a guide for treatment options such as infiltration or joint bleed drainage [7].

Ultrasonography also has some disadvantages: the most significant are operator dependency, which results in interobserver assessment variability, and the fact that specific training is required [7,8].

The aim of this study, therefore, is to compare the reliability of US evaluation of joint damage in

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haemophilic patients carried out by two raters with different levels of expertize: a radiologist and a non-radiologist.

Consecutive patients with haemophilia (all severities) were recruited at the Centre for Haemophilia and Congenital Bleeding Disorders of the IRCCS San Matteo General Hospital Foundation in Pavia, Italy. The study was approved by the local ethics committee and all patients gave informed consent.

We excluded patients with haemophilia C and other coagulopathies, and patients with joint damage due to other pathologies not related to haemophilia.

From a total of 59 male patients examined, we recruited 36 patients for the study: 9 patients did

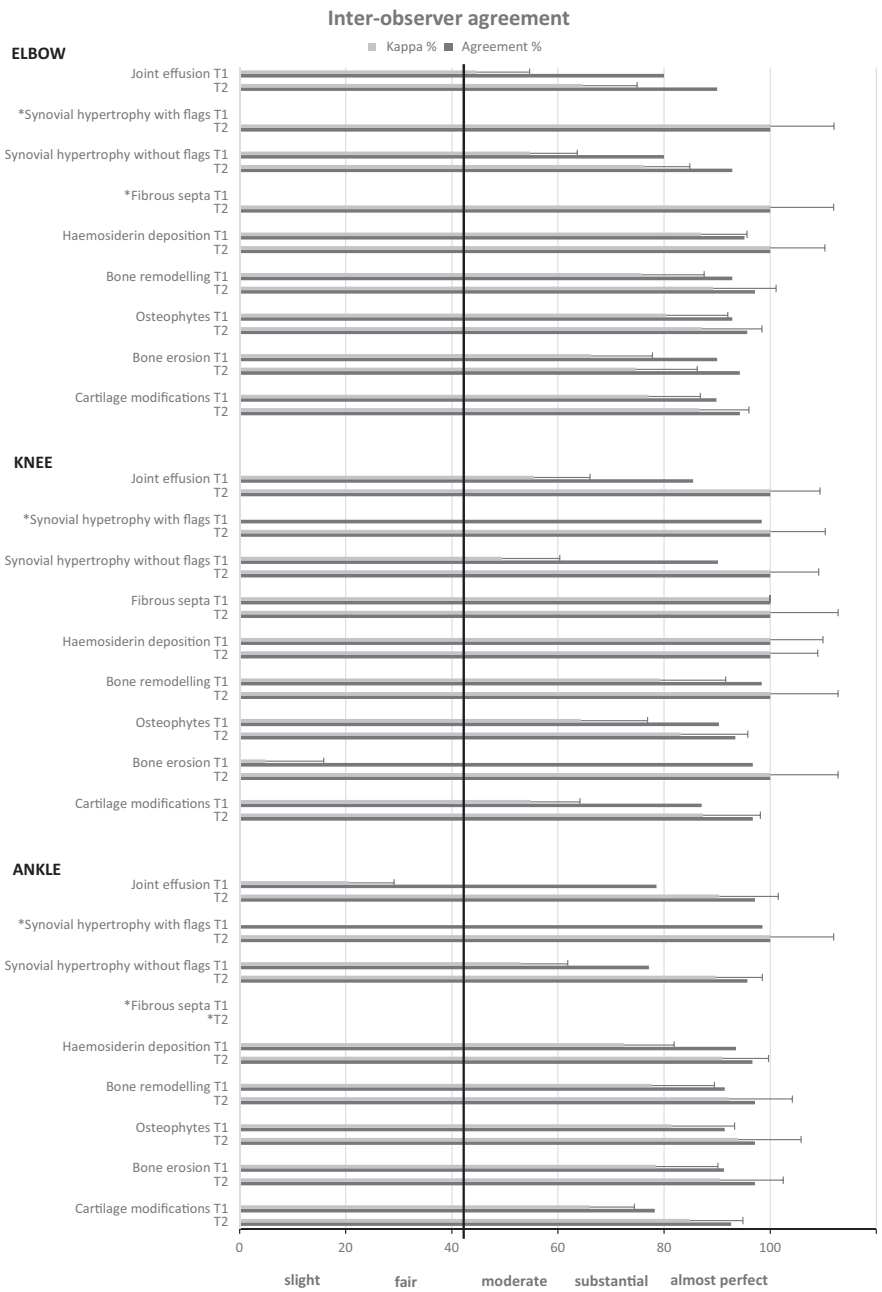


**Fig. 1.** Interobserver agreement. (*) means that *K* cannot be calculated. Standard error for *K* is shown. The vertical bar indicates agreement of 40%. Elbow: agreement is greater than 40% for all the considered variables at both T1 (2012) and T2 (2013). Overall, agreement is higher at T2. The variable 'joint effusion' has the lowest concordance. Knee: concordance is poor for the variable 'bone erosions' at T1. By T2, however, the correlation of this variable is almost perfect. Agreement is greater than 40% for all the other considered variables, at both T1 and T2. Overall, agreement is higher at T2. Ankle: concordance is poor for the variable 'joint effusion' at T1. At T2, however, this variable's correlation is excellent. Agreement is greater than 40% for all the other considered variables, at both T1 and T2. Overall, agreement is higher at T2.

not give informed consent, 11 patients were lost to follow-up (1 deceased), 2 patients had haemophilia C and 1 patient was excluded due to a diagnostic error.

The mean age of the study population was 33 ± 17 (range 6–70). Thirty-three patients had haemophilia A (11 mild, 2 moderate, 20 severe), and three had haemophilia B (1 mild, 2 severe).

Bilateral US of the elbow, knee and ankle joints was consecutively performed in all patients in the Physical Medicine and Rehabilitation Unit of the IRCCS San Matteo General Hospital Foundation in Pavia, Italy.

This is a 3-year study. In the first year (2011), the non-radiologist observer was trained in musculoskeletal ultrasonography, generic and specific to haemophilia patients, 8 h a week by three radiologists from the Institute of Radiology of the IRCCS San Matteo General Hospital Foundation, each of whom had more than 20 years of experience in musculoskeletal ultrasonography. Recruitment and the first US evaluation (T1) of the patients took place in the second year (2012). The second US evaluation (T2) and statistical analysis were carried out in the third year (2013).

Each patient was evaluated separately and independently by the same observers (C.M., D.G.) on the same day with the same US device, transducer and settings. Each observer was blinded to the interpretation of the other and, at T2, to the results of previous investigations.

Ultrasonographic evaluation was carried out using a real-time US scanner (MY LAB FIVE, Esaote, Genova and Florence, Italy) with a linear probe (7.5–12 MHz).

The elbow, knee and ankle joints of each patient were evaluated bilaterally, excluding joints previously treated with prosthesis replacement, arthrodesis or other types of surgery. Static and dynamic evaluation was carried out on all studied joints.

We used the ultrasonographic score proposed by Melchiorre *et al.* [9], which investigates the presence of HA considering the following variables: joint effusion, synovial hypertrophy and angiogenesis, fibrous septa, haemosiderin deposition, remodelling of bone, osteophytes, erosions and cartilage.

Positioning of the limb and transducer for image acquisition at each imaging plane, and the scanning sequence of elbows, knees and ankles adhered to the protocol suggested by Melchiorre *et al.* [9] and the Musculoskeletal Ultrasound Technical Guidelines of the European Society of Musculo Skeletal Radiology.

Interobserver agreement was assessed at T1 and T2.

Power of the study: in a test for agreement between two raters using the Kappa statistic, a sample size of 35 subjects achieves 86% power to detect a true Kappa value of 0.80 in a test of H0: Kappa = 0.40 vs. H1: Kappa <> 0.40 when, there are three categories with frequencies equal to 0.15, 0.25, and 0.60. This power calculation is based on a significance level of 0.05.

Quantitative variables were expressed as mean values and standard deviation (SD) as they were normally distributed (Shapiro–Wilk test); qualitative variables were summarized as counts and percentages.

Interobserver agreement was analysed using Cohen's kappa coefficient (with the standard error). The kappa-statistic measurement of agreement varies from 0 (no match) to 100 (perfect match) and takes into account agreement by chance. For intermediate values, Landis and Koch [10] suggest the following interpretation: below 0: poor; 0–20: slight; 21–40: fair; 41–60: moderate; 61–80: substantial; 81–100: almost perfect. If all ratings of all raters are equal, it is not possible to calculate the value of kappa. Data analysis was performed with STATA statistical package (release 13, 2013; Stata Corporation, College Station, TX, USA).

Each year, we evaluated the elbows, knees and ankles of 36 patients (amounting to an annual total of 202 joints): 70 elbows, due to one spontaneous arthrodesis and one fracture treated with an osteosynthesis; 63 knees, due to nine total knee replacement; 69 ankles, due to three arthrodesis.

Overall agreement was 94%; 91% in 2011, 97% in 2012. Overall *K* value was 71%; 53% in 2011, 88% in 2012. *K* values were lower for the ankle (66%) and higher for the knee (77%).

Concordance values between US evaluation performed by a radiologist observer and a non-radiologist observer are reported in the following graphs (Fig. 1). Although each joint in question was assessed bilaterally, a single value of concordance is expressed for each variable, considering right and left laterality together.

In conclusion, it could be useful to perform US evaluation at every clinical assessment of haemophilic patients. Our data show that US evaluation can be performed by a trained non-radiologist when it is not possible to have a radiologist performs a specialistic evaluation.

US could be a valid and reliable tool for trained non-radiologists to evaluate and monitor HA over time.

## Author contribution

C. Lisi, G. Di Natali, V. Sala, M. Canepari performed the research. C. Lisi, G. Di Natali, G. Gamba, C.Tinelli, E. Dalla Toffola designed the research study. C. Tinelli analysed the data and revised the paper. C. Lisi, G. Di Natali, V. Sala wrote the paper.

## Disclosures

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

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## Appendix

We scored the modifications of joints according to Melchiorre's US score (13) as follows:

1. Joint effusion: (absent = 0; small = 1; moderate = 2; large = 3).
2. Synovial hypertrophy with flags on PDUS (<3 flags = 1; >3 flags = 2).
3. Synovial hypertrophy without flags on PDUS: thickness measured in mm (score 1: <1.5 mm; score 2: 1.5–2.5 mm; score 3: >2.5 mm).
4. Fibrous septa: absent = 0; present = 1.
5. Haemosiderin deposition: it appears as a diffuse hyperechoic signal (absent = 0; small = 1; moderate = 2; large = 3).
6. Remodelling of bone: defined as joint surface irregularity and incongruence (absent = 0; present = 1).
7. Osteophytes: defined as marginal hypertrophic bone formation (absent = 0; present = 1).
8. Bone erosion: defined as a cortical 'break' with an irregular shape seen in the longitudinal or in the coronal plane (absent = 0; present = 1).
9. Cartilage damage: absent = 0; hyperechogenicity = 1; irregular profile = 2; calcification = 3.

# Self-infusion of prophylaxis: evaluating the quality of its performance and time needed


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Prophylactic replacement therapy is the cornerstone of treatment in severe haemophilia. Regular infusions with clotting factor concentrate have been proven effective to prevent bleeding, subsequent (joint) damage, and positively affect the impact of haemophilia on daily life [1]. Patients or parents of younger patients learn to infuse clotting factor concentrate in a peripheral vein (i.v.) or a central venous access device (CVAD) [2].

As even a single bleed may cause irreversible damage, prophylaxis requires lifelong adherence and well-developed self-management skills [3]. The UKHCDO guidelines (United Kingdom Haemophilia Centre Doctors Organisation) described that competence in venous access technique as an important aspect of successful prophylaxis [4]. In the Netherlands, these skills are learned in an individualized training course with an average of eight sessions (IQR: 4–14 visits) [2]. After


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ORIGINAL ARTICLE

# Focused extracorporeal shock wave therapy combined with supervised eccentric training for supraspinatus calcific tendinopathy

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## ABSTRACT

BACKGROUND: Extracorporeal shockwave therapy (ESWT) is effective in reducing shoulder pain and improving function in calcific supraspinatus tendinopathy. Eccentric exercise has been introduced as an effective treatment choice for Achilles tendinopathy, but poor evidence exists about its role in the treatment of rotator cuff tendinopathy.
AIM: To investigate if adding a supervised eccentric training of the shoulder abductor muscles could improve the outcome of ESWT.
DESIGN: Pre-post intervention pilot study with matched control-group.
SETTING: Outpatient, University Hospital.
POPULATION: Twenty-two subjects affected by painful supraspinatus calcific tendinopathy.
METHODS: The study-group was assigned to receive focal ESWT (f-ESWT) plus a supervised eccentric training (SET) of the shoulder abductor muscles. The matched control-group received f-ESWT only. The post-treatment assessment at follow-up (T1) was performed nine weeks after the enrollment (T0). We assessed shoulder pain and function by the means of a numeric rating scale (p-NRS) and a DASH scale. As secondary outcome, we measured the isometric strength of the abductor muscles of the affected shoulder using a handheld dynamometer.
RESULTS: At T1, we recorded a significant decrease in pain ($P<0.001$) and an improvement in upper limb function ($P<0.001$) in both groups. However, we observed no statistical differences in favor of the study-group, in terms of p-NRS and DASH total score. A mild increase (+13% from baseline) of the maximum isometric abduction strength was noticed in the study group at T1.
CONCLUSIONS: Our findings did not support the hypothesis that adding a supervised eccentric training of the shoulder abductor muscles could improve the outcome (pain and function) of shock wave therapy.
CLINICAL REHABILITATION IMPACT: Our study confirmed that f-ESWT is effective in reducing shoulder pain and improving function in calcific supraspinatus tendinopathy. Adding a supervised eccentric training, focused on the abductor muscles, was useful to improve maximum isometric abduction strength, but appeared to give no advantage in the short-term outcome of shock wave therapy.

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**Key words:** Tendinopathy - Rotator cuff - Lithotripsy - Exercise.

Rotator cuff calcific tendinopathy, with particular involvement of the supraspinatus tendon, represents one of the most relevant causes of chronic shoulder pain between 30 and 60 years of age.[1, 2] Although the precise mechanism of injury leading to tendinopathy remains unknown, mechanical overloading is actually considered the major cause.[3, 4] The current gold standard in the therapy of tendinopathy of the rotator cuff remains a conservative approach.[5, 6] Efficacy on pain control of corticosteroid injection and non-steroidal

anti-inflammatory drugs is proven but usually limited in time.[6, 7] Among the remaining conservative treatments, extracorporeal shockwave therapy (ESWT) appeared to provide beneficial effects in various insertional tendinopathies and bone disorders.[8-10] ESWT is effective in reducing shoulder pain and improving function in patients affected by supraspinatus calcific tendinopathy.[8-20] Conversely, there is lack of scientific evidence confirming the efficacy of other physical therapies, such as ultrasound and laser therapy.[2, 5, 6] Supervised exercise has been shown to be as effective as surgery, in case of shoulder impingement syndrome, in reducing pain and improving function in both short and long-term perspective.[21, 22] In the last decade, eccentric exercise has been introduced as an effective treatment choice for Achilles tendinopathy,[23-26] but poor evidence exists about its role in the treatment of rotator cuff tendinopathy.[27, 28] Jonsson, Bernhardsson and Camargo reported, in subsequent non-randomized studies, an improvement in pain and function after eccentric trainings of the rotator cuff in chronic painful subjects with shoulder impingement syndrome.[29-31] In a randomized controlled study, Maenhout concluded that adding an eccentric exercise to a traditional rotator cuff training resulted in a higher gain in abduction isometric strength.[32] Until now, a single study analyzed the combined effect of shockwave therapy and eccentric exercise, but on Achilles tendinopathy only.[33] The same author previously demonstrated, in a randomized controlled trial on patients with calcific insertional Achilles tendinopathy, that shockwave therapy showed better clinical outcome than eccentric training.[34]

The aim of this pilot study is therefore to investigate if adding a supervised eccentric training of the shoulder abductor muscles could improve the outcome of focal ESWT (f-ESWT), with respect to shoulder pain, function and strength, in a population affected by supraspinatus calcific tendinopathy.

## Materials and methods

In a single-institution pre-post intervention study with matched control group, conducted from March 2013 to July 2015 in an outpatient rehabilitative setting, we collected data on subjects affected by monolateral painful supraspinatus tendinopathy. Inclusion criteria were adult age (18 to 65 years), duration of shoulder pain of six weeks or longer, clinical signs of sub-acromial impingement, normal passive glenohumeral range of movement and sonographic evidence of rotator cuff calcific tendinopathy, with the supraspinatus tendon lonely or predominantly affected. Exclusion criteria were general contraindication to ESWT (pacemaker, pregnancy, bleeding disorders or anticoagulant drug usage, cancer in the focal area), history of rheumatologic disease, previous fractures or surgery in the affected shoulder, full thickness tear of the rotator cuff tendons, frozen shoulder, clinical signs of cervical radiculopathy, corticosteroid injections or other conservative therapies (except pharmacological pain treatments) since the onset of the current pain episode.

The study-group was assigned to receive f-ESWT plus a supervised eccentric training (SET) of the shoulder abductor muscles; the control-group received f-ESWT only. The patients' allocation was made according to the criterion of age and sex homogeneity: for each case enrolled in the study-group, we enrolled a ±5-year-old control of the same gender in the matched control-group. At the beginning of the study, the first eligible patient was assigned to the study-group, then we progressively assigned the following eligible patients to the control-group, if "matchable" with one of the subjects already treated in the study-group, or to the study-group if not. A post-treatment evaluation (follow-up T1) was performed nine weeks after the first f-ESWT session (T0).

Participants signed their consent in accordance with the indications of the local ethical committee.

### *Procedures*

Before the enrollment, a specialized-PRM physician performed a clinical and an ultrasound examination of the affected shoulder in patients eligible for inclusion. The first f-ESWT session occurred one week after the enrolment. A device powered by a piezoelectric generator (PIEZOSON 100PLUS, Richard Wolf GmbH, Knittlingen, Germany) was used for f-ESWT. Participants underwent the treatment in sitting position, the affected shoulder lying on the side in internal rotation. At the beginning of each treatment session, the humeral enthesis of the supraspinatus tendon was targeted through a non-inline sonographic focusing, using a linear probe (7.5-

12 MHz) connected to an ultrasound scanner (MyLab™ Five, Esaote SpA, Genoa, Italy). All patients received 1700 pulses (frequency = 4 Hz) with an energy flux density of 0.15 mJ/mm$^2$ once a week for three consecutive weeks. We placed a coupling gel between the probes and the skin.

Both groups were asked for a pain therapy-free period (one week) before f-ESWT and to avoid pain-exacerbating activities throughout the study protocol. In case of transient severe pain exacerbations, we allowed the use of paracetamol (1000 to 2000 mg daily) during the treatment period, but we did not proceed to monitor its assumption by means of a journal. We asked the participants not to attend to any other treatment during the study protocol.

After the third f-ESWT session, participants assigned to the study-group started a six-week SET.

They attended four supervised physiotherapy sessions, twice a week for the first two weeks of training.

From the first session, they were educated to reproduce daily, at home, an eccentric exercise for the abductors muscles of the affected shoulder, using an elastic resistance band, as visualized in Figure 1. In particular, they were trained to perform the eccentric phase of the exercise at a speed of 5"/repetition, maintaining a full can modality (thumb up). We added stretching exercises for the anterior and posterior region of the shoulder before and after each training session. Each time the study-group participants returned to the clinic to perform the remaining three supervised sessions, a physiotherapist checked out the technique of execution, increasing the number of the series and the elastic resistance, in order to keep the intensity of the exercise through a mild pain (a value lower than 4 on a pain numeric rating scale). During the first two weeks of training, the exercise dosage provided for a progression from one to three series of 10 repetitions, with a pause of one minute between the series. During the residual four weeks, we asked them to continue the program daily, without supervision, at home.

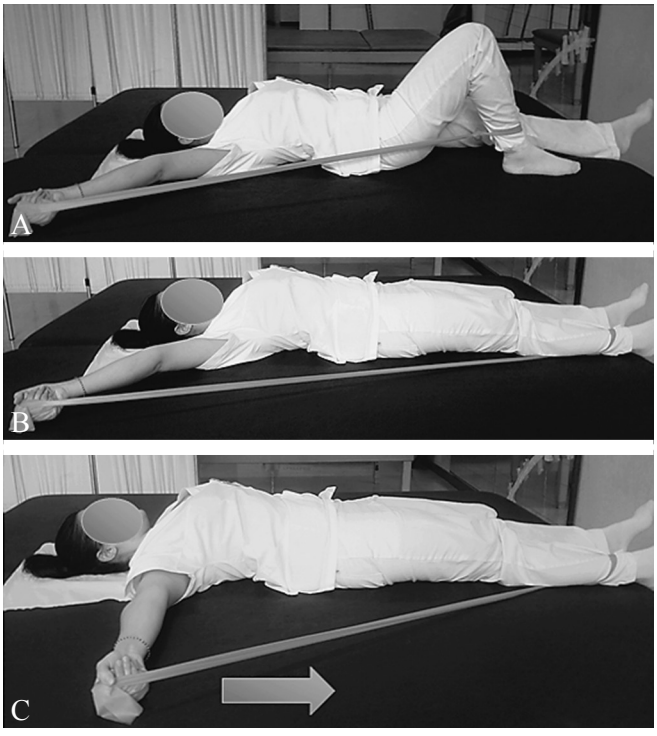


Figure 1.—Eccentric full-can abduction exercise: A) starting position; B) the elastic band is tensed up; C) eccentric phase.

*Outcome assessment*

At baseline, we recorded demographics, pain duration and localization (side) of the pathology.

At T0 and T1, we studied all participants for shoulder pain and function as primary outcome. We analyzed pain and function respectively by the means of a pain-on-movement numeric rating scale (p-NRS), ranging from zero ("no pain") to 10 ("the worst imaginable pain"), and a DASH scale, a self-administered questionnaire designed to measure functional performances and symptoms of the upper limb.[35-37] The DASH scale ranges from zero (no functional limitation) to 100 (complete shoulder inability). Each item of the DASH scale ranges from one (no difficulty) to five (unable to complete the task). We were particularly interested in two items, which reflect typically sub-acromial pain-exacerbating active movements: item number 6 ("place an object on a shelf above your head") and item number 15 ("put on a pullover sweater"). As secondary outcome, we measured the isometric strength of the abductor muscles of the affected shoulder, using a handheld dynamometer (TRACKER freedom wireless v.5 software, JTECH Medical). We performed the test, at T0 and at T1 follow-up, with patients in sitting position, the upper limb at 40° of shoulder abduction from the trunk, in neutral humeral rotation and with the elbow extended. During the test,

we used standardized verbal instructions to achieve the maximal isometric effort, as the examiner pushed down the affected limb with the dynamometer at the forearm level. The examiner repeated each measurement twice and registered the maximum value of isometric strength expressed (Isom Fmax), measured in newtons (N).

### *Statistical analysis*

The Shapiro-Wilk test was used to analyze the normal distribution of quantitative variables; the results were expressed as mean values and standard deviation (SD) as they were all normally distributed; qualitative variables were summarized as counts and percentages. *t*-test for paired data was used to analyze pre-post therapy differences and *t*-test for independent data for comparisons between groups.

A regression model for repeated measures was use to adjust for the p-NRS in the comparisons of Isom Fmax at T0. A $P<0.05$ was considered statistically significant and all tests were two-sided. Data analysis was performed with STATA statistical package (release 14, 2015; Stata Corporation, College Station, TX, USA).

## Results

Twenty-six patients fulfilled the inclusion criteria during the observation period. We excluded two of them because of a recent corticosteroid injection treatment; two further patients refused to participate. Finally, we enrolled 22 participants. Data about basic demographics, pain duration and localization (side) of the pathology are shown in Table I. At baseline, we observed no statistical differences between groups in terms of side affected (P=0.39) and duration of pain (P=0.58). No patient was lost at 9-week follow-up.

All the participants felt the f-ESWT unpleasant but tolerable. No patients stopped the therapy because of the pain. We recorded no local side effect; one patient referred a mild and transient dizziness at the end of the third session of treatment. The eccentric loading was well tolerated by the patients of the study-group, who reported mild shoulder pain during exercise, always promptly disappearing at rest.

TABLE I.—*General assessment data and outcome measures at baseline (T0) and at follow-up (T1).*

| Variables | Control group | Study group | P value |
|---|---|---|---|
| Sample | 11 | 11 | |
| Sex female/male | 7/4 | 7/4 | 1 |
| Mean age, years | 49.5±8.6 | 50.3±9.1 | 0.8309 |
| Pain onset, months | 6.2±6.7 | 4.8±3.3 | 0.5724 |
| Painful side, right/left | 5/6 | 8/3 | 0.387 |
| p-NRS at T0 | 6.4±1.6 | 5.3±1.5 | 0.113 |
| p-NRS at T1 | 2.9±2.7 | 1.4±1.1 | 0.1014 |
| DASH total score at T0 | 39.1±14.6 | 34.8±14.6 | 0.5005 |
| DASH total score at T1 | 18.8±16.8 | 16.1±9.7 | 0.6440 |
| DASH item6 at T0 | 3.5±0.7 | 3.2±1 | 0.4826 |
| DASH item6 at T1 | 2±1 | 2.1±0.6 | 0.7735 |
| DASH item15 at T0 | 3±0.9 | 2.5±1 | 0.3360 |
| DASH item15 at T1 | 2±1.3 | 1.7±0.7 | 0.5109 |
| Isom $F_{max}$ at T0, newtons | 125.6±37 | 101.5±44 | 0.2000 |
| Isom $F_{max}$ at T1, newtons | 129.4±25.1 | 116.7±51.5 | 0.4765 |

Data is presented as mean ± SD.
p-NRS: pain Numeric Rating Scale; DASH: Disability of the Arm, Shoulder and Hand scale; Isom $F_{max}$: maximum value of isometric abduction strength.

### *Primary outcome: pain and function*

Group data for all outcome measures at T0 and T1 are reported in Table I. We observed no statistical differences between groups in terms of p-NRS (P=0.11) and DASH total score (P=0.5) at baseline. Comparisons between groups (expressed in delta values T0–T1), are shown in Table II and in Figure 2.

At follow-up, we recorded a statistically significant decrease in pain-NRS ($P<0.001$) and an improvement in upper limb function ($P<0.001$), measured by DASH total score, in both groups (Table I). However, we observed no statistical differences in favor of the study-group, in terms of p-NRS (P=0.65) and DASH total score (P=0.84), as visualized in Table II and Figure 2. DASH item 6 and 15 followed the same trend as DASH total score (Tables I, II).

TABLE II.—*Outcome measures: pre-post treatment differences (T0-T1).*

| Variable (T0–T1 difference) | Control group | Study group | P values |
|---|---|---|---|
| p-NRS | 3.45±2.07 | 3.82±1.6 | 0.6496 |
| DASH total score | 20.32±23.01 | 18.79±9.97 | 0.8425 |
| DASH item6 | 1.4±1.17 | 1.11±0.78 | 0.5413 |
| DASH item15 | 1.3±1.42 | 0.89±0.6 | 0.4318 |
| Isom $F_{max}$, newtons | -3.82±29.99 | -15.11±18.97 | 0.3409 |

p-NRS: pain Numeric Rating Scale; DASH: Disability of the Arm, Shoulder and Hand scale; Isom $F_{max}$: maximum value of isometric abduction strength.

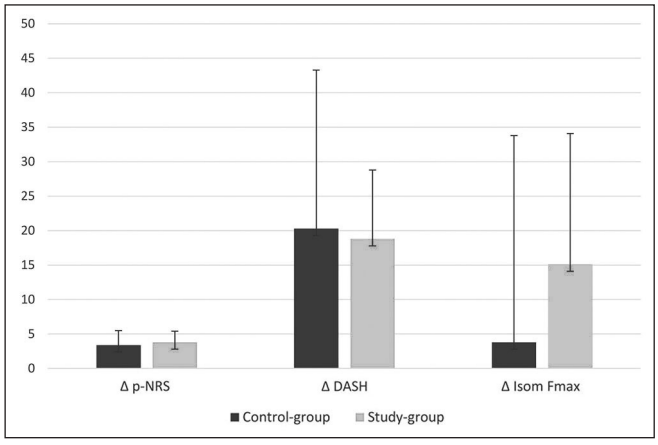


Figure 2.—Comparison between groups expressed in ΔT0-T1. No differences between groups were found in the statistical analysis. An increase of 13% from the baseline maximum isometric abduction strength was observed in the study group at T1 (P=0.34).

*Secondary outcome: strength*

Values of maximum isometric strength in shoulder abduction are expressed in Table I.

At T0, the study-group expressed slightly lower values of maximum isometric strength in the affected shoulder than the control-group, but this difference was not statistically significant (P=0.2). The regression model excluded that such baseline difference might have depended on the p-NRS values. A mild increase of maximum isometric strength in shoulder abduction at 40° (+13% from baseline) was noticed in the SET-performing group at T1, however not statistically significant (Figure 2).

## Discussion

Our findings did not support the hypothesis that adding a supervised eccentric training of the shoulder abductor muscles could improve the outcome (pain and function) of f-ESWT in the treatment of calcific supraspinatus tendinopathy. Our study confirmed that f-ESWT is effective in reducing shoulder pain and improving function, but we observed no statistical differences in favor of the SET-performing group after treatment. Nevertheless, we found a mild but not significant increase (+13% from baseline) in the maximum isometric abduction strength after the SET.

Our findings should be read to the light of the following pending arguments. First, few studies have been published about the effectiveness of an eccentric training program for rotator cuff tendinopathy, so poor evidence exists about the use of this type of exercise. In most cases, those studies enrolled subjects affected by sub-acromial impingement syndrome, excluding patients with tendon tears, but not clearly defining the cause of sub-acromial pain.[27-37] Second, the way of action of both shockwaves therapy [38-40] and eccentric training [28, 41, 42] is based on a mechano-transduction pathway but the precise biological mechanism of action is not yet fully understood.[40] Third, even in presence of a potential rationale of a combined use of shockwaves and eccentric training, a single study analyzed the clinical outcome of such a strategy. In 2009, Rompe reported better results (therapeutic success in 82% of the cases) of a combined use of eccentric training plus radial ESWT *versus* eccentric loading alone (56%) in the treatment of mid-portion Achilles tendinopathy.[33] More recently, Kvalvaag proposed a new study protocol to investigate the efficacy of a combined use of radial ESWT and supervised exercises (including eccentric exercises) in patients affected by sub-acromial shoulder pain,[43] but further studies are needed to confirm the efficacy of eccentric exercise in improving the outcome of ESWT in this field.

With regard to the exercise protocol, we chose a supervised eccentric exercise for shoulder abductor muscles only, in order to keep the training simple and home reproducible and to improve patients' compliance. We selected the supine position in order to obtain a better scapulothoracic joint stabilization and a better upper-spine muscles relaxation than the upright position, relying on the fact that the elastic band and the full-can modality would have reduced the impingement-effect linked to the supine position. The option of a full-can modality of exercise was justified by the fact that the supraspinatus activity is optimized in this position, with reduced deltoid recruitment.[44, 45] There is a lack of evidence regarding those factors which might influence the outcome of an eccentric training, in particular about the duration. Previous works are heterogeneous in terms of dosage, duration (6 to 12 weeks) and modality of exercise: Jonsson focused on a supraspinatus-deltoid eccentric strengthening lasting 12 weeks,[29] Bernhardsson on a supraspinatus plus infraspinatus 12 weeks eccentric training,[30] Camargo proposed a 6 weeks eccentric isokinetic training for shoulder abductors, reporting a

significant decrease in pain and disability.[31] A single randomized controlled trial by Maenhout pointed-out that adding an eccentric exercise to a traditional rotator cuff training resulted in a higher gain (15%) in abduction isometric strength, but was not more effective in decreasing pain and improving function after 12 weeks of training.[32] In comparison to the literature, the shorter duration (six weeks) of our exercise protocol should not have influenced the outcome, since Maenhout reported a significant increase in isometric abduction strength at the 6th week of training, but not from the 6th to the 12th week. He also reported that most of the clinical improvement also took place during the first six weeks of training. In fact, the performance of our study-group at follow up is in line with the results reported by Maenhout.[32] The lack of a longer follow-up, instead, could have negatively influenced our understanding of the SET outcome, masking the longer benefits of this type of exercise, since the supposed biological effects usually require a longer period to consolidate.[28]

Finally, it might be interesting to compare the maximum isometric strength values of our sample to the healthy population. In 2009, a Danish group of authors reported a set of reference measures for maximal isometric muscle strength of the major body muscles. If we try to approximate a comparison, taking into account the technical differences in measurement and adjusting for the lever arm, the maximum isometric abduction strength values of our population at baseline appear to be about in line with those of the youngest group of Danneskiold-Samsøe.[46]

### *Limitations of the study*

The present study has several limitations. First, the small number of patients enrolled. Given the small size and the not randomized design of this pilot trial, the present falls under the "hypothesis-concerning" type of study. Second, as mentioned earlier, the lack of a longer follow-up prevented further comparisons with the previously published literature and the evaluation of the impact of our exercise program on the medium and long-term. However, one of the main problem in the conservative management of tendinopathy is the long duration of the treatments, so that most patients are usually poorly compliant. For such reason, and expressing an everyday practice need, we focused our approach on treating and evaluating our sample in a short-term outcome. Third, the investigators could not be blinded to the group assignment, but the influence of their expectations about the outcome was probably marginal, since both groups showed marked improvement over time.

## Conclusions

f-ESWT is effective in reducing shoulder pain and improving function of patients affected by calcific supraspinatus tendinopathy. Adding a supervised eccentric training, focused on the abductor muscles, brought to a mild improvement in maximum isometric abduction strength, but appeared to give no advantage in the short-term outcome (pain and function) of shockwave therapy.

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# Observational multicentric study on chronic sciatic pain: clinical data from 44 Italian centers

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**Abstract. – OBJECTIVE: To provide information on the clinical presentation of sciatic neuropathy and its management in a real-world setting, and to analyze the effects of a multimodal approach based on the association of physical and pharmacological therapy.**

**PATIENTS AND METHODS: A multicentric observational prospective study was conducted in 44 Italian tertiary centers specialized in Physical Medicine and Rehabilitation, Orthopedics, Neurology, Neurosurgery, and Rheumatology. To develop a shared management of LPB with sciatica, a dedicated clinical record was proposed to collect data about diagnosis, treatment, and outcomes. Pain, disability, and quality of life were recorded trough validated questionnaires at baseline and after a two-month follow-up.**

**RESULTS: 394 patients (age, mean ± SD 55.7 ± 14.1 years, 57.1% females) with chronic LBP and sciatica were enrolled in the study. The characteristics of the selected group showed a certain variability in the clinical presentation. At baseline, patients received several different therapeutic options among physical, pharmacological and neurotrophic treatments. A subgroup of 312 patients was treated with a combination of neurotrophic agents containing alpha-lipoic acid (ALA). After a two-month follow-up, a general improvement in both perceived pain and functional disabilities was observed. A significant improvement ($p < 0.001$) in the Pain Numeric Rating Scale (NRS), Roland e Morris Disability Questionnaire (RMDQ) and Brief Pain Inventory (BPI) Italian short version was observed.**

**CONCLUSIONS: Sciatic neuropathy is a multifaceted condition managed by means of a wide spectrum of therapeutic options. The results of this study suggest that a multimodal approach based on the association of ALA with physical and pharmacological therapies can be beneficial in the treatment of LBP with sciatica.**

*Key Words:*
Mesh terms) low back pain, Sciatic neuropathy, Complementary therapies, Pain management, Alpha-lipoic acid.

## Introduction

Chronic low back pain (LBP) with sciatica is defined as pain and discomfort, localized below the costal margin and above the inferior gluteal folds, with referred leg pain persisting for at least 12 weeks[1-5].

Sciatic neuropathy is among the most common peripheral neuropathies, since it is estimated to affect 5 in every 10000 Western adults[6]. Thus, it represents a social problem both in terms of patients' suffering and health costs for treating the progression of the disease. More generally speaking, LBP of at least moderate intensity and duration has an annual incidence in the adult population of 10-15% and a prevalence of 15-30%. It becomes increasingly frequent in patients older than 65 years. Therefore, a relevant number of elderly people, approximately one out of every three to four, suffers from low back pain[3].

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Chronic LBP with sciatica shows a broad range of clinical manifestations and consequences on patients' lives, from a preserved functionality in spite of pain to a severe disability or an interference with sleep by persistent back pain and radicular pain and paresthesia[1-5]. Chronic LBP with sciatica is a quite common cause of long-term disability in middle-aged people and, due to its resistance to pharmacological and surgical interventions, requires a multimodal and multidisciplinary approach[1,5,7].

The economic burden of chronic LBP, in general, is relevant, spine diseases being fifth in terms of hospitalization/inpatients costs and first as a cause of absenteeism and burden of disability[8].

The optimal management of chronic LBP with sciatica is still a matter of debate. A large panel of therapeutic options is available[5,9-12].

Surgery doesn't seem to be a first choice treatment for radicular neuropathy, except the cases in which it can't be avoided. A systematic review with meta-analysis of cohort studies revealed that patients with sciatica still experience pain and disability 5 years after surgery[7].

Non-pharmacologic therapies for chronic LBP with sciatic neuropathy include acupuncture, exercise therapy, massage therapy, yoga, cognitive behavioral therapy or progressive relaxation, spinal manipulation, and intensive interdisciplinary rehabilitation. Although the level of supporting evidence for the different therapies varies from fair to good, at the moment there is no consensus about a first choice treatment[9-11].

Notably, recent evidence suggests that a multimodal and multidisciplinary approach involving orthopedics, physiatrists, rheumatologists, and neurologists may be the most appropriate for sciatic neuropathy. That approach also implies a detailed knowledge of pathophysiological and clinical data in order to obtain a 360-degree framework of the condition and to address the priority needs in its management.

This study focused on patients with chronic LBP with sciatica, is part of a wider project aimed at proposing an appropriate and shared management at a national level of all patients with peripheral compression neuropathy (e.g. carpal tunnel syndrome and sciatic neuropathy)[12]. Thus, the Management of Peripheral Neuropathies Study Group, composed of Specialists in Physical and Rehabilitation Medicine, Orthopaedics, Neurology, Neurosurgery, Rheumatology, Anesthesiology and Pain Medicine, has designed (March-May 2012) and conducted for the following 14 months (May 2012-June 2013) this observational study aimed at providing an updated picture of chronic LBP with sciatica, including the clinical characteristics of the patients (etiology, location, severity, duration) and the management of the disease. Participating centers were outpatients care services in hospitals or in centers for outpatients care, both public or private, spread throughout Italy.

To develop a shared management of LPB with sciatica, a dedicated clinical record was proposed to collect data about diagnosis, treatment, and outcomes.

The main objectives were to determine the clinical and demographic characteristics of patients, the concomitant diseases and the response to the multimodal treatment proposed.

As regards diagnosis, we included in the clinical report the etiology, location, clinical characteristics of the disease, a complete physical examination including Lasegue's and Wassermann's maneuvers and osteotendinous reflexes, in order to propose a single shared protocol for the diagnosis of the compression neuropathy.

Previous diagnostic procedures, previous and ongoing treatments (physical therapy, pharmacological therapy or neurotrophic agents) were also included in the clinical report.

The Study Group decided to recommend the use of neurotrophic agents, and in particular of alpha-lipoic acid (ALA), because of the increasing evidence of effectiveness in neuropathic pain and considering the good tolerability of the treatment[12-25].

ALA is an antioxidant that has been recently identified as a first-choice treatment for chronic neuropathic pain[13], because of the proven effectiveness compared to placebo in the treatment of neuropathic pain[13-22].

ALA exerts a protective effect on the nerve fibers, acting on the nerve inflammation and the progression of nerve damage. Furthermore, it does not interfere with other pharmacological treatments and is generally well tolerated[21], so we decided to recommend its use as an adjuvant for the treatment of neuropathy in the patients enrolled in the study.

The study group recommended a multimodal treatment, including physical, pharmacological and neurotrophic therapies, but decided not to give a precise indication about which treatment to select within the various options. This decision was taken in order to observe the current man-

agement of sciatic pain in a real world setting.

At the same time, the study was designed to provide a feedback on the efficacy of current clinical practice and of the multimodal approach proposed, through the registration of clinical data at baseline and at the end of the follow-up. The Study Group selected the parameters to be evaluated and the questionnaires to be administered on the basis of the international literature. Among the questionnaires, the Numeric Rating Scale (NRS)[26,27] was adopted by Pain in Europe (http://www.paineurope.com), the European survey about chronic pain; the Roland and Morris Disability Questionnaire (RMDQ)[28,29] is aimed at evaluating disability; the Brief Pain Inventory-short form (BPI)[30,31] is focused on measuring pain and its interference on activities of daily living; the Short Form-12 Health Survey (SF-12)[32-34] is used to evaluate the quality of life.

## Patients and Methods

### Study Design

The observational study was carried out between May 2012 and June 2013, enrolling 394 consecutive patients with chronic LBP with sciatica followed in 44 specialized Italian centers participating in the Management of Peripheral Neuropathies Study Group (see the list of participating centers).

The main objectives were to determine (i) the pattern of this condition; (ii) the concomitant diseases and the characteristics of patients; (iii) the response to treatments.

Patients of both genders older than 18 years with chronic (>12-week duration) LBP with sciatica were included.

A model of dedicated clinical record was developed to homogeneously collect the most relevant data about diagnosis, monitoring, and outcomes.

The study was conducted in accordance with the current guidelines of good clinical practice (GCP) regulations relating to clinical trials and the Declaration of Helsinki and was approved by the local Ethics Committee.

Informed consent was obtained from all the patients after explaining the aim of the work and the relevance of the questionnaires.

### Data Collection

At baseline, the following information was collected: demographic data (age, gender, anthropometric data); lifestyle and work activity and their relation to the condition; referral from general practitioners (GP) or specialists; comorbidities; aetiology, location, and clinical characteristics of the compression neuropathy; complete physical examination including Lasegue's and Wassermann's maneuvers and osteotendinous reflexes; previous diagnostic procedures, previous and ongoing treatments (physical therapy, pharmacological therapy, or neurotrophic agents used for at least 10 days consecutively).

Patients were asked to state if they considered the previous treatments effective or not.

### Pain Assessment

The pain was assessed by means of standardized questionnaires whose Italian translations have been previously validated: the NRS, the RMDQ, the Italian version of the BPI, and the SF-12 questionnaire.

The NRS[26,27] is a segmented numeric horizontal bar on which patients select a whole number (from 0 "no pain" to 10 "worst possible pain") that best reflects the intensity of their pain at rest and on movement. It has become a widely used instrument for pain screening and is ubiquitous as a screener in many health care environments.

The RMDQ[28,29] is a patient-reported measure of back pain which explore the patients' ability to perform 24 activities of daily living. Items are scored to yield a total score from 0 "no disability" to 24 "maximum disability". It is used to assess the patients' subjective rating of perceived disability and helps the clinician to address the functional limitations of the patients. Scores were categorized as follows:

- **From 0 to 9:** sub-acute or chronic LBP with mild disability (may be managed by the general practitioner);
- **From 10 to 13:** sub-acute or chronic LBP with a moderate disability;
- **> 14:** sub-acute or chronic LBP with severe disability (a multimodal and multidisciplinary management is needed).

The BPI[30] is a self-administered assessment tool which measures pain interference. It consists of 9 items measuring interference, experience of pain on the current day, and localization of pain occurrence. Scores are assigned on a scale from 0 "does not interfere" to 10 "completely interferes". Its short form[31] is used for clinical trials and translated in foreign languages, as in the case of the short Italian version named BQVD, Breve Questionario per la Valutazione del Dolore).

Scores were categorized as follows:
• Factor 1 – Pain intensity (range 0-50);
• Factor 2 – Affective interference (range 0-30);
• Factor 3 – Activity interference (range 0-30).

The SF-12[32-34] is a generic health status measure including 12 items which yield a profile of functional health and well-being. It is recommended for self-administration, brevity, simplicity, validity and reliability.

### Statistical Analysis

Quantitative variables were reported as mean ± standard deviation (SD) and range, qualitative variables as absolute and relative frequencies. Data were summarized in tables and figures as appropriate.

The data collected were analyzed by standard descriptive statistics.

The intragroup differences in NRS, RMDQ, BPI (baseline *vs.* end of follow-up) were assessed by means of paired *t*-test. Differences have been considered significant where $p < 0.05$.

As regards the SF-12, we only reported the variation of the answers to each item, so as to point out which ones were more influenced by the treatments.

No direct comparison of the treatments was performed.

No missing data have been replaced and no replacement policy has been implemented; as a matter of fact, the analysis fully reflects the observed values.

The statistical analysis has been performed using the software SPSS Statistical Package, version 16.0 (SPSS Inc., Chicago, IL, USA).

## Results

### Patients

Baseline characteristics of the 394 patients (age, mean ± SD 55.7 ± 14.1 years, 57.1% females) with chronic LBP with sciatica enrolled in the study are reported in Table I. Among all patients, 12.4% were menopausal and 2% pregnant women.

For the majority of patients (63.5%) time since the initial diagnosis ranged from 3 to 12 months, while for the others initial diagnosis was made more than one year before enrolment. The most common comorbidities were osteoarthritis (28.2%), diabetes (19.3%), osteoporosis (17%), thyroid disorders (10.9%) and rheumatoid arthritis (3.6%).

### Physical Examination

Following physical examination, patients were classified as having: sciatica (82.7%, n = 326), low back pain (9.4%, n = 37), cruralgia (3.6%, n = 14). The diagnosis after the physical examination was missing in 17 (4.3%) patients.

As regards semiotic maneuvers a positivity in Lasègue's test was observed in 68.8% of patients, and a positivity in Wassermann's test in 30.2% of patients. Osteotendinous reflexes were normal in 47.2%, reduced in 36.3%, absent in 3.5% of patients. Muscle wasting was observed in 26.7% of patients.

49.7% of patients reported diurnal paresthesia and 45.9% reported nocturnal paresthesia.

### Instrumental Diagnostic Procedures

Considering diagnostic imaging, 52.3% (n = 206) of patients underwent conventional X-ray,

**Table I.** Demographic and clinical characteristics of patients at baseline.

| | All patients (N = 394) |
|---|---|
| Gender | no. (%) |
| - Female | 225 (57.1%) |
| - Male | 169 (42.9%) |
| Age (years) | 55.7 ± 14.1 |
| mean ± SD (range) | (25-87) |
| Body weight (kg) | 73.4 ± 12.9 |
| mean ± SD (range) | (47-120) |
| Height (cm) | 168.7 ± 8.5 |
| mean ± SD (range) | (140-197) |
| BMI (kg/m$^2$) | 26.1 ± 4.2 |
| mean ± SD (range) | (17.9-43.8) |
| BMI categories (reference values) | no. (%) |
| - Underweight (< 18.5 kg/m$^2$) | 2 (0.5%) |
| - Normal weight (18.5-24.9 kg/m$^2$) | 165 (41.9%) |
| - Overweight (25-29.9 kg/m$^2$) | 143 (36.3%) |
| - Obesity (≥ 30 kg/m$^2$) | 62 (15.7%) |
| - ND | 22 (5.6%) |
| Smoking habit | no. (%) |
| 1. No | 226 (57.3%) |
| 2. Yes | 122 (31.0%) |
| - ND | 46 (11.7%) |
| Work activity no. (%) | no. (%) |
| 1. Blue collar | 59 (15.0%) |
| 2. White collar | 103 (26.1%) |
| 3. Homeworker | 82 (20.8%) |
| 4. Retiree | 79 (20.1%) |
| 5. Others | 63 (16.0%) |
| - ND | 8 (2.0%) |
| Work-related chronic back pain | no. (%) |
| 1. No | 169 (42.9%) |
| 2. Yes | 80 (20.3%) |
| 3. Uncertain | 106 (26.9%) |
| - ND | 39 (9.9%) |

ND: Not determined.

**Table II.** Baseline treatments before enrolment.

| | Patients treated (no.) | Clinical response | | |
|---|---|---|---|---|
| | | No | Yes | ND |
| Physical therapy no. (%) | | | | |
| Corset | 89 | 25 (28.1%) | 51 (57.3%) | 13 (14.6%) |
| Laser/Carbon dioxide laser | 66 | 34 (51.5%) | 19 (28.8%) | 13 (19.7%) |
| Electroanalgesia | 36 | 21 (58.3%) | 6 (16.7%) | 9 (25.0%) |
| Ultrasound | 51 | 27 (52.9%) | 14 (27.5%) | 10 (19.6%) |
| TENS | 85 | 44 (51.8%) | 27 (31.8%) | 14 (16.5%) |
| Diadynamic | 42 | 23 (54.8%) | 7 (16.7%) | 12 (28.6%) |
| Others | 24 | 13 (54.2%) | 8 (33.3%) | 3 (12.5%) |
| **Pharmacological therapy** no. (%) | | | | |
| NSAIDs | 226 | 86 (38.1%) | 97 (42.9%) | 43 (19.0%) |
| Corticosteroids (oral) | 88 | 19 (21.6%) | 52 (59.1%) | 17 (19.3%) |
| Corticosteroids (infiltration) | 43 | 7 (16.3%) | 19 (44.2%) | 17 (39.5%) |
| Paracetamol | 94 | 49 (52.1%) | 37 (39.4%) | 8 (8.5%) |
| Opioids | 42 | 6 (14.3%) | 25 (59.5%) | 11 (26.2%) |
| Others | 29 | 14 (48.3%) | 11 (37.9%) | 4 (13.8%) |
| **Neurotrophic therapy** no. (%) | | | | |
| ALA | 37 | 6 (16.2%) | 24 (64.9%) | 7 (18.9%) |
| Carnitine | 46 | 16 (34.8%) | 9 (19.6%) | 21 (45.7%) |
| B complex vitamins | 61 | 21 (34.4%) | 9 (14.8%) | 31 (50.8%) |
| Others | 9 | 4 (44.4%) | 4 (44.4%) | 1 (11.1%) |

57.4% (n = 226) nuclear magnetic resonance (NMR), and 17.5% (n = 69) computed tomography (CT). Electromyography was performed in 10.7% (n = 42) of patients.

### Final Diagnosis

All in all, the most prevalent conditions were herniated disc in 53.8% (n = 212) of patients and disc space narrowing in 11.9% (n = 47).

### Baseline Treatments Before Enrolment

Previous treatments before enrolment had been prescribed by the GPs in 62.9% of patients, by a specialist in 32.5%. The response to previous treatments, classified in three main categories (physical therapy, pharmacological therapy, and neurotrophic therapy), is reported in Table II. Physical therapy interventions were associated to low response rates (in general less than a third of patients) with the exclusion of corset (57.3% of responders), TENS (31.8%), laser/carbon dioxide laser (28.8%), and ultrasound (27.5%). Response rates to pharmacological therapy ranged between 39.4% and 59.5% with the different options. Among neurotrophic medications, only ALA obtained satisfactory response rates (64.9%).

### Prescribed Treatments

The prescribed treatments at baseline, classified in the same three main categories, are reported in Table III.

A wide variability in the interventions was apparent. The most prescribed physical treatments were TENS (28.9%) and corsets (26.1%).

**Table III.** Prescribed treatments.

| | All patients No. (%) |
|---|---|
| **Physical therapy** | |
| Corset | 103 (26.1%) |
| Laser/Carbon dioxide laser | 60 (15.2%) |
| Electroanalgesia | 34 (8.6%) |
| Ultrasound | 47 (11.9%) |
| TENS | 114 (28.9%) |
| Diadynamic | 28 (7.1%) |
| Others | 104 (26.4%) |
| **Pharmacological therapy** | |
| NSAIDs | 135 (34.3%) |
| Corticosteroids (oral) | 59 (15.0%) |
| Corticosteroids (infiltration) | 33 (8.4%) |
| Paracetamol | 101 (25.6%) |
| Opioids | 75 (19.0%) |
| Others | 40 (10.2%) |
| **Neurotrophic agents** | |
| ALAnerv ON | 226 (57.4%) |
| ALA600 SOD | 86 (21.8%) |
| Carnitine | 27 (6.9%) |
| B complex vitamins | 14 (3.6%) |
| Others | 10 (2.5%) |

As regards pharmacological therapy, NSAIDs and paracetamol (34.3% and 25.6%, respectively) were more frequently used than corticosteroids (oral 15% and infiltration 8.4%). A considerable amount of cases (19%) required opioids.

Among neurotrophic agents, the most prescribed were ALAnerv ON® (ALA 300 mg, gamma-linolenic acid, GLA, 180 mg, honokiol 27 mg, selenium 25 µg, vitamin B1 1.05 mg, vitamin B2 1.2 mg, vitamin B5 4.5 mg, vitamin B6 1.4 mg, vitamin E 7.5 mg, and selenium 25 µg; Alfa Wassermann, Bologna, Italy) and ALA600 SOD® (ALA 600 mg, superoxide dismutase, SOD, 140 IU/day, vitamin E 7.5 mg, and selenium 25 µg; Alfa Wassermann, Bologna, Italy). The associations have been prescribed to 57.4% and 21.8% of patients, respectively. The use of carnitine or B complex vitamins was relatively limited, accounting for approximately 10%.

At the final evaluation after a two-month follow-up, the compliance to treatments and the need for dose changing were recorded.

Physical therapy was completed as planned in 65.2% of patients.

Considering pharmacological therapy, daily administration schedule was unchanged in 72.1% of patients and withdrawn in 1.5%; while a dose increase was needed in 9.4% of patients, and a dose reduction in 4.1%.

Considering neurotrophic therapy, daily administration schedule was unchanged in 78.7% of patients and withdrawn in 2.5%; while a dose increase was needed in 4.1% of patients, and a dose reduction in 3.8%.

An analysis of patients' characteristics according to the prescribed treatments is reported in Table IV. The analysis focuses on the association of physical, pharmacological and neurotrophic therapies and their prescription according to age, gender and intensity of pain (mild, moderate, severe according to the NRS scale). We observed a good adherence to the recommendation of the Study Group to adopt a multimodal strategy, with a greater prescription of all the three categories of treatments (neurotrophic, pharmacological and physical) in the patients with the higher levels of pain.

### Pain and Disability Scores

At the end of the study, a general improvement in both perceived pain and functional disabilities was observed.

Specifically, the NRS (cases assessed, baseline *vs.* end of follow-up 360 *vs.* 341) significantly improved in both pain at rest (baseline *vs.* end of follow-up, mean ± SD 6.6 ± 2.2 *vs.* 2.1 ± 1.8, $p < 0.001$) and pain on movement (7.6 ± 1.9 *vs.* 2.6 ± 1.8, $p < 0.001$).

**Table IV.** Prescribed treatments according to patients' characteristics and pain intensity.

| | | Prescribed therapy | | | | |
|---|---|---|---|---|---|---|
| | NO NT (Phys T or Phar T or both) | NT | NT + Phys T | NT + Phar T | NT + Phys T + Phar T | Total |
| **Patients No.** | **33** | **25** | **44** | **87** | **205** | **394** |
| **Age** | | | | | | |
| < 65 years | 24 (75.0%) | 15 (60.0%) | 29 (67.4%) | 63 (73.3%) | 149 (73.0%) | 280 (71.8%) |
| ≥ 65 years | 8 (25.0%) | 10 (40.0%) | 14 (32.6%) | 23 (26.7%) | 55 (27.0%) | 110 (28.2%) |
| **Gender** | | | | | | |
| - Female | 17 (53.1%) | 18 (72%) | 23 (54.8%) | 45 (51.7%) | 119 (58.6%) | 222 (57.1%) |
| - Male | 15 (46.9%) | 7 (28.0%) | 19 (45.2%) | 42 (48.3%) | 84 (41.4%) | 167 (42.9%) |
| **NRS at rest** | | | | | | |
| Mild (1-3) | 2 (7.7%) | 4 (16.6%) | 5 (12.2%) | 8 (10.1%) | 7 (3.7%) | 26 (7.3%) |
| Moderate (4-6) | 9 (34.6%) | 10 (41.7%) | 17 (41.5%) | 18 (22.8%) | 67 (35.7%) | 121 (33.8%) |
| Severe (7-10) | 15 (57.7%) | 10 (41.7%) | 19 (46.3%) | 53 (67.1%) | 114 (60.6%) | 211 (58.9%) |
| **NRS on movement** | | | | | | |
| Mild (1-3) | 0 (0%) | 1 (4.2%) | 1 (2.4%) | 1 (1.2%) | 7 (3.7%) | 10 (2.8%) |
| Moderate (4-6) | 1 (4.0%) | 10 (41.6%) | 16 (39.1%) | 16 (19.8%) | 35 (18.5%) | 78 (21.6%) |
| Severe (7-10) | 24 (96%) | 13 (54.2%) | 24 (58.5%) | 64 (79.0%) | 147 (77.8%) | 272 (75.6%) |

NT: Neurotrophic Therapy; Phys T: Physical Therapy; Phar T: Pharmacological Therapy.

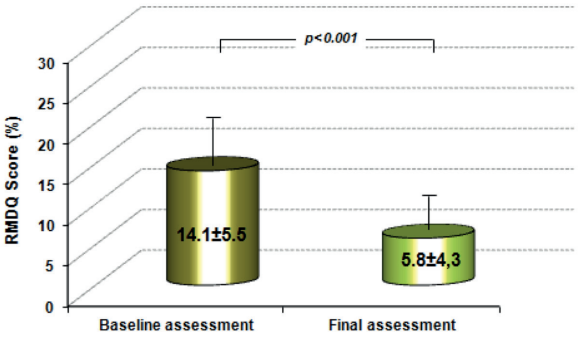


**Figure 1.** Roland and Morris Disability Questionnaire (RMDQ) at baseline and at the end of treatment.

The RMDQ mean proportion of positive responses (cases assessed 203 *vs.* 192) passed from 14.1 ± 5.5% to 5.8 ± 4.3% ($p < 0.001$) (Figure 1). For all the items a trend towards a reduction (ranging from –3% to –59%) was observed.

An improvement in all three factors of BPI short Italian version was recorded (factor 1, pain intensity 284 ± 93 *vs.* 111 ± 84; factor 2, affective interference 150 ± 76 *vs.* 47 ± 57; factor 3, activity interference 186 ± 65 *vs.* 74 ± 59, $p < 0.001$ for all). Pain relief from any treatment in the last 24 hours was reported more frequently at the end of the study (39.6 ± 20.6% *vs.* 60.4 ± 29.2%, $p < 0.001$).

An improvement in all the SF-12 items was observed (Table V).

## Discussion

This observational study with descriptive purposes provides a "real life" representation of chronic LBP with sciatica in Italy, in terms of patients' characteristics and therapeutic interventions.

The group of patients selected is likely representative of the whole population suffering from this condition: young-elderly, the onset of signs and symptoms generally occurring in the last 12 months, a broad range of causes, clinical presentation and radiologic features.

However, the presence of pain and disability is a quite common aspect, confirming the high burden on health and on quality of life of chronic LBP with sciatica.

Similarly, a wide variability in the management of the disease is apparent. This is consistent with the fact that guidelines do not express homogenous and straightforward recommendations[9-11].

Notably, according to the Italian Diagnostic, Clinical and Therapeutic pathway for patients with LBP[35], the first level approach should include, in both acute and chronic conditions, counseling, modification of daily life, and active lifestyle, followed by conventional palliative medical treatment and rehabilitation. This latter aimed at functional recovery by means of several different interventions (exercises, cognitive-behavioral therapy, back school and multidisciplinary treatments).

Unfortunately treatment guidelines usually refer to LBP with or without sciatica as a unique pathology. So, as the targets are both LBP and neuropathic sciatic pain, a multimodal strategy targeting both kinds of pain should be followed.

At the moment considering the individual patient's characteristics, including not only the symptoms but also the level of disability, is adviced. Therefore, there is consensus about a multimodal and multidisciplinary approach, focused on the pathophysiology of the disease, and more specifically acting on two main directories: pain and disability.

As far as the pharmacological treatments are concerned, when choosing the pharmacological therapy, typically anti-inflammatory and analgesic medications, the average age of patients with chronic LBP and the even increasing prevalence in the older population have to be taken into account to prevent a higher occurrence of side effects and reach an acceptable harm to benefit ratio. To this aim, pathogenetic therapies represent a promising option and, accordingly, their prescription is recommended in neuropathic pain[13,14].

A recent Post-hoc analysis of the NATHAN I trial, in which patients with diabetic neuropathy were treated with ALA 600 mg/day by oral route for 4 years, highlighted the significant effectiveness of ALA in particular in older people (>65 years), with a significant reduction in the Neuropathy Impairment Score (NIS) *vs.* placebo[21].

Among neuropathic mechanisms of sciatica pain, oxidative stress which develops after the peripheral neuropathic lesion is acknowledged as a relevant factor responsible for neuropathic pain, leading to the activation of an inflammatory pathway involving the whole peripheral nerve up to the spinal dorsal horn, and, subsequently, of microglia[36-39]. This process may result in spine sensitization and in chronic neuropathic pain[14,38].

Recently, ALA and superoxide dismutase (SOD), another antioxidant agent endowed with

**Table V.** SF-12 Health Survey Questionnaire at baseline and at the end of treatment.

| | Baseline | Final |
|---|---|---|
| **1. In general, would you say your health is** | | |
| Excellent | 0.6% | 1.3% |
| Very good | 7% | **23.9%** |
| Good | **43.6%** | **50.3%** |
| Fair | **31.4%** | **21.4%** |
| Poor | **17.4%** | 3.1% |
| ***Does your health now limit you in these activities? If so, how much?*** | | |
| **2. Moderate activities** | | |
| Yes, limited a lot | **61.6%** | 9.9% |
| Yes, limited a little | 34.3% | **62.3%** |
| No, not limited at all | 4.1% | 27.8% |
| **3. Climbing several flights of stairs** | | |
| Yes, limited a lot | 48.3% | 5.6% |
| Yes, limited a little | 42.4% | 54.9% |
| No, not limited at all | 9.3% | 39.5% |
| ***During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?*** | | |
| **4. Accomplished less than you would like** | | |
| Yes | **84.8%** | 38.3% |
| No | 15.2% | **61.7%** |
| **5. Were limited in the kind of work or other activities** | | |
| Yes | **91.2%** | **58%** |
| No | 8.8% | 42% |
| ***During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?*** | | |
| **6. Accomplished less than you would like** | | |
| Yes | **78.4%** | 29.4% |
| No | 21.6% | **70.6%** |
| **7. Did work or activities less carefully than usual** | | |
| Yes | **57.3%** | 13.9% |
| No | 42.7% | **86.1%** |
| **8. During the past 4 weeks, how much did pain interfere with your normal work (including both housework and work outside the home)?** | | |
| Not at all | 1.2% | 4.4% |
| A little bit | 2.3% | 38.1% |
| Moderately | 26.9% | **45%** |
| Quite a bit | **48.5%** | 10% |
| Extremely | 21.1% | 2.5% |
| ***How much of the time during the past 4 weeks*** | | |
| **9. Have you felt calm and peaceful?** | | |
| All of the time | 1.2% | 12.7% |
| Most of the time | 15.3% | **36.1%** |
| A good bit of the time | 7.1% | 20.8% |
| Some of the time | **45.3%** | 22.2% |
| A little of the time | 22.9% | 6.3% |
| None of the time | 8.2% | 1.9% |
| **10. Did you have a lot of energy**? | | |
| All of the time | 1.8% | 7.1% |
| Most of the time | 5.9% | 22.4% |
| A good bit of the time | 5.9% | 23.1% |
| Some of the time | 29.3% | 35.2% |
| A little of the time | 40% | 9.6% |
| None of the time | 17.1% | 2.6% |

*Table continued*

**Table V *(Continued)*.** SF-12 Health Survey Questionnaire at baseline and at the end of treatment.

| | Baseline | Final |
|---|---|---|
| **11. Have you felt downhearted and depressed?** | | |
| All of the time | 9.3% | 2.5% |
| Most of the time | 14% | 3.8% |
| A good bit of the time | 20.5% | 5.7% |
| Some of the time | **32.2%** | 28.9% |
| A little of the time | 19.3% | **44.7%** |
| None of the time | 4.7% | 14.4% |
| **12. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?** | | |
| All of the time | 7.6% | 2.5% |
| Most of the time | 19.9% | 2.5% |
| Some of the time | 33.3% | 7.5% |
| A little of the time | 31% | 44.4% |
| None of the time | 8.2% | 43.1% |

anti-inflammatory properties[40,41], have been proven effective in the management of diabetic neuropathy[42], low back pain[43], and chronic neck pain[44].

Therefore, antioxidant agents like ALA and SOD may be a useful choice in the multimodal treatment strategy for chronic LBP patients, since they can contribute to pain control due to their prevalently anti-inflammatory action[42-44].

The benefit of ALA in association with neurotrophic agents has been demonstrated in patients with chronic conditions characterized by an impairment in the nerve fiber function. Clinical trials on patients with radiculopathies and carpal tunnel syndrome show that the combination of ALA and GLA, a polyunsaturated n-3 (omega-3) fatty acid, exerts a synergistic positive effect on symptoms and peripheral nerve fiber conduction[19,20,24]. Neurotrophic agents such as GLA, honokiol and vitamin B complex have been used in association with ALA to improve sensory-motor function[12,23-25].

Antioxidant and neurotrophic agents may contribute to pain control, thus allowing to reduce analgesic medications and, as a consequence, to improve the safety profile of the therapeutic strategy adopted.

On the other hand, the effectiveness of physical therapies is controversial because of the lack of high quality clinical trials[9-12,45,46]. Transcutaneous electrical nerve stimulation (TENS) is based on the delivering of electrical stimulation to the underlying nerves via electrodes placed over the intact skin surface near the source of maximal pain.

Four high-quality randomised controlled trials (585 patients) comparing TENS with placebo for chronic low-back pain have been published. Due to conflicting evidence, it is unclear if TENS is beneficial in reducing back pain intensity[45].

It has to be highlighted that any intervention has to be considered in the framework of a multidisciplinary approach in order to address the various pathogenetic mechanisms with an appropriate multimodal treatment.

On the base of these considerations, our Study Group decided to recommend a multimodal approach including pharmacological, physical and neurotrophic treatments, with particular consideration to ALA, that has the higher degree of evidence among neurotrophic agents in neuropathic pain. We decided not to recommend a particular kind of pharmacological or physical treatment. The reason for this is that patients enrolled suffered from different levels of pain (mild, moderate or severe) and could be suffering from various comorbidities, thus a unique drug could not be recommended for all the patients. Furthermore, as regards physical therapies there is not a clear indication from literature and the participating centers could not have all the instruments for the various physical therapies available, so we decided to let the centers have freedom of choice in the pharmacological and physical treatments on the basis of patients' characteristics.

In this investigation, we observed a clinically significant improvement in symptoms, disability and quality of life.

Key results of the study are in our opinion the general and considerable improvement in both perceived pain (NRS and BPI) and functional disability (RMDQ), that can be considered a remarkable result, considering that the most effective drugs used alone for neuropathic pain have a NRS pain reduction *vs.* placebo ranging

from -1.30 for gabapentin to -1.06 for duloxetine[17]. Furthermore, we observed a good adherence to the recommendation of the Study Group to adopt a multimodal strategy, with a greater prescription of all the three categories of treatments (neurotrophic, pharmacological and physical) in the patients with the higher levels of pain.

This report has several limitations, as it is an observational study which comprises a wide variety of treatments and can't demonstrate the effectiveness of a particular treatment or of an association of treatments. It can only suggest that the association of ALA with pharmacological and physical therapies produce a clinically significant improvement in pain, functional disability and quality of life in patients suffering from LBP with sciatica.

Another limitation is that, although the Study group recommended to include in the study only patients suffering from LBP with sciatica, a little percentage of the patients enrolled didn't have a clear diagnosis of sciatic neuropathy. Despite this data, we considered all the patients included by the centers for the analysis, in the certainty that they all were endowed with a neuropathic component in LBP.

## Conclusions

This study describes a likely representative population of patients suffering from chronic LBP with sciatica whose conditions were carefully assessed by means of standardized and validated questionnaires and followed prospectively for 2 months. Since a multimodal and multidisciplinary approach was adopted, a broad range of therapeutic options were used, which resulted in a general improvement in both perceived pain and functional disabilities. These results suggest that a multimodal approach can be beneficial in the treatment of LBP with sciatica.

### Notes

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### Conflict of Interest

The Authors declare that they have no conflict of interests.

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# Treatment of knee osteoarthritis: platelet-derived growth factors vs. hyaluronic acid. A randomized controlled trial

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## Abstract

**Objective:** Aim of this trial was to compare efficacy of activated platelet-rich plasma against hyaluronic acid as intra-articular injections to people with osteoarthritis of the knee.

**Design:** Phase-2 randomized controlled trial, with blind patients and outcome assessors.

**Setting:** Outpatient rehabilitation service; years 2011–2013.

**Subjects:** Patients with knee osteoarthritis grades 2–3 at magnetic resonance imaging (MRI) were included after consent and randomized. Target sample size was 25 patients per group.

**Interventions:** Patients received three activated platelet-rich plasma (intervention group) or hyaluronic acid (controls) intra-articular injections at 4-week intervals.

**Main measures:** Main outcome measure was proportion of patients with >1 grade improvement at six months from last injection, as assessed by a radiologist blind to study group. Patients were evaluated over time clinically and with functional scales (Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Lysholm, Tegner, American Knee Society Score (AKSS), Lequesne, visual analogue scale (VAS) for pain).

**Results:** Overall, 30 patients were randomized to intervention and 28 to control group. For primary outcome, 28 patients (29 knees) in the intervention and 22 (25 knees) in the control group were available. Patients with at least 1 grade improvement at repeat MRI were 14 (48.3%) in the intervention and 2 (8%) in the control group ($P < 0.003$). Improvement in symptoms and functional scales was consistently higher in the intervention group. No side-effects were observed in either group.

**Conclusion:** Activated platelet-rich plasma reduces articular damage as evident at MRI, as soon as six months after treatment; it reduces pain and improves patient's function and overall quality of life.

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Osteoarthritis of the knee, platelet-derived growth factors, randomized controlled trial

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## Introduction

Pathogenesis of osteoarthritis is complex and is linked to the limited ability of cartilage to repair, given its limited vascularisation.[1,2] The knee is the most commonly involved joint.[1]

Many pharmacological and non-pharmacological treatments have been proposed.[3,4] Intra-articular injections of hyaluronic acid are effective in improving symptoms and slow disease progression, but are not able to reverse the damage mechanism and trigger cartilage healing.[5,6] Biological, regenerative, minimally invasive treatments such as platelet-rich plasma have been investigated.[7,8] Growth factors included in platelet-rich plasma could stimulate cartilage repair, normalize synovial fluid viscoelasticity, induce a correction in tissue damage, improve articular function, control pain and ameliorate quality of life.[8,9] Recently, a stable cartilage damage was demonstrated in 73% of patients 1 year after the treatment with platelet-rich plasma, thus suggesting that this treatment might be able to stop the damage mechanism.[10] This treatment also appears safe.[11]

Primary aim of this trial was to assess, among patients with grade II/III osteoarthritis of the knee, efficacy (as determined by improvement at magnetic resonance imaging (MRI) six months after the first injection) of three intra-articular injections of platelet lysate when compared to hyaluronic acid. Additional objectives were to compare the treatment groups in terms of several functional scales and of number of adverse events.

## Methods

This study was designed as a Phase-2, two-parallel-arm, randomized controlled trial, where patients, radiologist, clinical outcome assessors and statistician were blinded to study treatments. Prior to starting patients' enrolment, the study was approved by the institutional ethic review board (protocol number: 28914/2009). The anticipated study duration was three years (January 2011–December 2013). No change in study methods intervened during study conduct (ClinicalTrials.gov, Identifier: NCT02958761). Full protocol is available upon request.

All consecutive patients referred to the Physical Medicine and Rehabilitation Unit of Policlinico San Matteo Foundation for osteoarthritis of the knee in the study period were screened for inclusion. Eligibility criteria were as follows:

- Grade II/III osteoarthritis of the knee demonstrated at MRI, according to Shahriaree Classification System – Modified[12] (Table 1, web only);
- Age >18 years;
- No previous osteoarthritis treatment with local hyaluronic acid or steroid injections;
- Life expectancy >1 year (i.e. no cancer, no end-stage liver disease, no-end-stage kidney disease, no heart failure New York Heart Association (NYHA) class III or IV);
- No ongoing pregnancy;
- Ability to understand and complete clinical and functional scales;
- No known allergy to hyaluronic acid;
- No acute bacterial skin and soft structure infection of the knee;
- Written consent.

Patients were then randomized into one of the treatment groups; if a patient had both knees affected, both were treated with the allocated study treatment. The patient's allocation ratio was 1:1. The randomization list was prepared by means of the ralloc procedure in Stata (version 10), with blocks (dimension of blocks 4-6-8). Concealment of allocation was obtained by maintaining the randomization list at the Clinical Epidemiology Unit

**Table 1.** Baseline patients' and knees' characteristics.

| Characteristic | Category/ description | Platelet lysate ($n = 30$ patients, 31 knees) | | Hyaluronic acid ($n = 28$ patients, 31 knees) | |
|---|---|---|---|---|---|
| Gender[a] | Males | 20 | 67% | 16 | 57% |
| Age (years)[a] | Mean (SD) | 53.5 | (15.1) | 57.1 | (10.0) |
| Laterality | Right | 17 | | 13 | |
| VAS | Mean (SD) | 6.28 | (0.59) | 5.40 | (0.36) |
| WOMAC pain | Mean (SD) | 6.6 | (0.81) | 5.04 | (0.51) |
| WOMAC rigidity | Mean (SD) | 2.6 | (0.45) | 2.32 | (0.28) |
| WOMAC ADL | Mean (SD) | 27.80 | (2.45) | 21.16 | (1.65) |
| Overall WOMAC | Mean (SD) | 36.96 | (3.33) | 28.48 | (2.22) |
| AKSS | Mean (SD) | 73.04 | (3.22) | 77.08 | (2.03) |
| Lysholm | Mean (SD) | 61.96 | (3.44) | 70.28 | (2.17) |
| Tegner | Mean (SD) | 3.04 | (0.32) | 3.6 | (0.23) |
| Lequesne | Mean (SD) | 11.16 | (0.85) | 9.00 | (0.58) |
| Flexion (angle degrees) | Mean (SD) | 123.4 | (2.98) | 126.8 | (1.97) |
| Complete extension | Yes | 31 | 100% | 31 | 100% |

VAS: visual analogue scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; ADL: activities of daily living; AKSS: American Knee Society Score.
Data are *n* (%) unless otherwise specified.
[a]Data at patient's level.

by the study statistician, who allocated each consecutive patient to treatment A or B. The clinicians administering the injections were unblinded; in case of bilateral knee osteoarthritis, both knees were treated with the treatment to which the patient had been allocated.

Patients in the intervention group received three autologous platelet-rich plasma plus calcium gluconate (as activator) intra-articular injections at four-week intervals. Briefly, at the Immunohaematology and Transfusion Service, on each scheduled visit, 20 mL of autologous whole blood was sampled from each patient and 2 mL Anticoagulant Citrate Dextrose Solution, Solution A was added directly through the syringe as anticoagulant; finally, the vial was gently centrifuged at 900 r/min for seven minutes. Platelet-rich plasma was collected. The platelet-rich plasma vial plus activator was immediately shipped to the rehabilitation unit, where intra-articular injection was performed by an experienced physiatrist.

Patients in the control group received three intra-articular hyaluronic acid (20 mg/2 mL; Hyalgan; Fidia, Abano Terme, Italy) injections at the same intervals by the same study staff. It was not possible to blind injectors for the different look of the treatments being compared. The infiltration technique used for both groups was the superolateral approach into the suprapatellar pouch.[13,14] After iodopovidone-base disinfection, a 21-gauge needle is ideal for knee injections with a 5-mL syringe was used.

For the superomedial approach, the patient lies supine with the knee almost fully or fully extended with a thin pad support underneath the knee to facilitate relaxation. Under ultrasound guidance in longitudinal section at the quadriceps tendon, the suprapatellar receps is localized; the clinician's thumb is used to gently rock and then stabilize the patella, the probe is rotated 90° and the needle is inserted laterally between the iliotibial band and the vastus lateralis muscle, directed to the centre or the probe.

Active flexion and extension of the knee was recommended after the injection, and the patient was observed in a supine position for 10–15 minutes, to ensure there were no adverse reactions, and was then discharged home without further recommendations or limitations. Patients were also allowed to take their pharmacological treatment for pain.

Six months after the last infiltration, MRI was repeated and assessed by a radiologist blind to study group. The radiologist scored each articular component (patellar front, patellar rear, tibial medial and tibial lateral) according to Shahriaree Classification System–modified (Table 1, web only).[12] For each knee at each time, the maximum grade was used. Primary end-point for each knee was improvement, from baseline, by at least one grade the maximum MRI score at six months.

At baseline (prior to treatment), at 15 days from the last injection, at six months from the last infiltration and at one year, all patients were clinically evaluated by a clinician blind to treatment group for articular angle, visual analogue scale (VAS) for pain and a number of functional scales: Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC; which measures pain, stiffness and disability in osteoarthritis),[15,16] Lequesne Scale (which measures the impairment in function, caused by pain),[17,18] Lysholm and Tegner Scales (which measure pain, joint block, instability and activity) and American Knee Society Score (AKSS) scale[19,20] (which allows a global evaluation specifically for the knee).

All study data were recorded on a paper case report form and then imputed into a database build with Microsoft Access by dedicated medical personnel. The target sample size was 25 patients per group and was calculated on the basis of a 50% patients improving at least one grade at the six-month MRI in the treatment group vs. a 10% improvement in the control group, to be detected with power 90% and alpha error 5% by means of a two-tailed chi-square test. No interim analyses were planned.

Descriptive statistics were produced for demographic, clinical and laboratory characteristics of enrolled patients and knees. Mean and standard deviation are presented for normally distributed variables, median and interquartile range for non-normally distributed variables and number and percentages for categorical variables. Groups were compared with parametric or nonparametric tests, according to data distribution, for continuous variables and with Fisher exact test for categorical variables. Also, to compare groups, taking into account that some patient had two knees treated, logistic regression models with clustering per patient were used. Multilevel mixed models were used to assess trend over time of secondary end-points (clinical and functional scales); random effects were patient, knee and slope over time, and interaction of group with time was the fixed effect. To achieve normality, Box–Cox transformation was applied whenever relevant (however, for readability, plots were produced in the original scale). In all cases, two-tailed tests were used. Statistical significance was set at 0.05. Whenever relevant, 95% confidence intervals (CIs) were calculated.

## Results

Of the 30 patients randomized to treatment group and the 28 to control group, 28 (1 with bilateral involvement, that is, 29 knees) and 22 patients (3 with bilateral involvement, that is, 25 knees) received the allocated intervention (Figure 1). No patient switched between treatment groups. Complete data at six months (primary end-point) were available for all knees. Therefore, 29+25 knees (28+22 patients) were evaluated in the primary analysis.

No relevant baseline differences between the two groups were observed (Table 1).

The number of patients (and knees) with at least 1 grade improvement at the MRI six months after last injection was 14 (48.3%, 95% CI: 29.4–67.5) in the treatment group and 2 (8%, 95% CI: 1.0–26.0) in the control group ($P<0.003$; Table 2 and Figure 2). Some patients even achieved complete *restitution ad integrum* of cartilage (Figure 3, web only).

Changes over time in terms of symptoms and functional scales were consistently better in the treatment group than the control group, reaching statistical significance for activity of daily living and total WOMAC, AKSS and Lequesne scale (Table 3; Figure 4, web only). No side-effects were observed in either group.

## Discussion

We found that activated platelet-rich plasma reduces articular damage as evident at MRI, as soon as six months after treatment. To our knowledge, this is the first study demonstrating efficacy of activated platelet-rich plasma on a strong clinical end-point such as

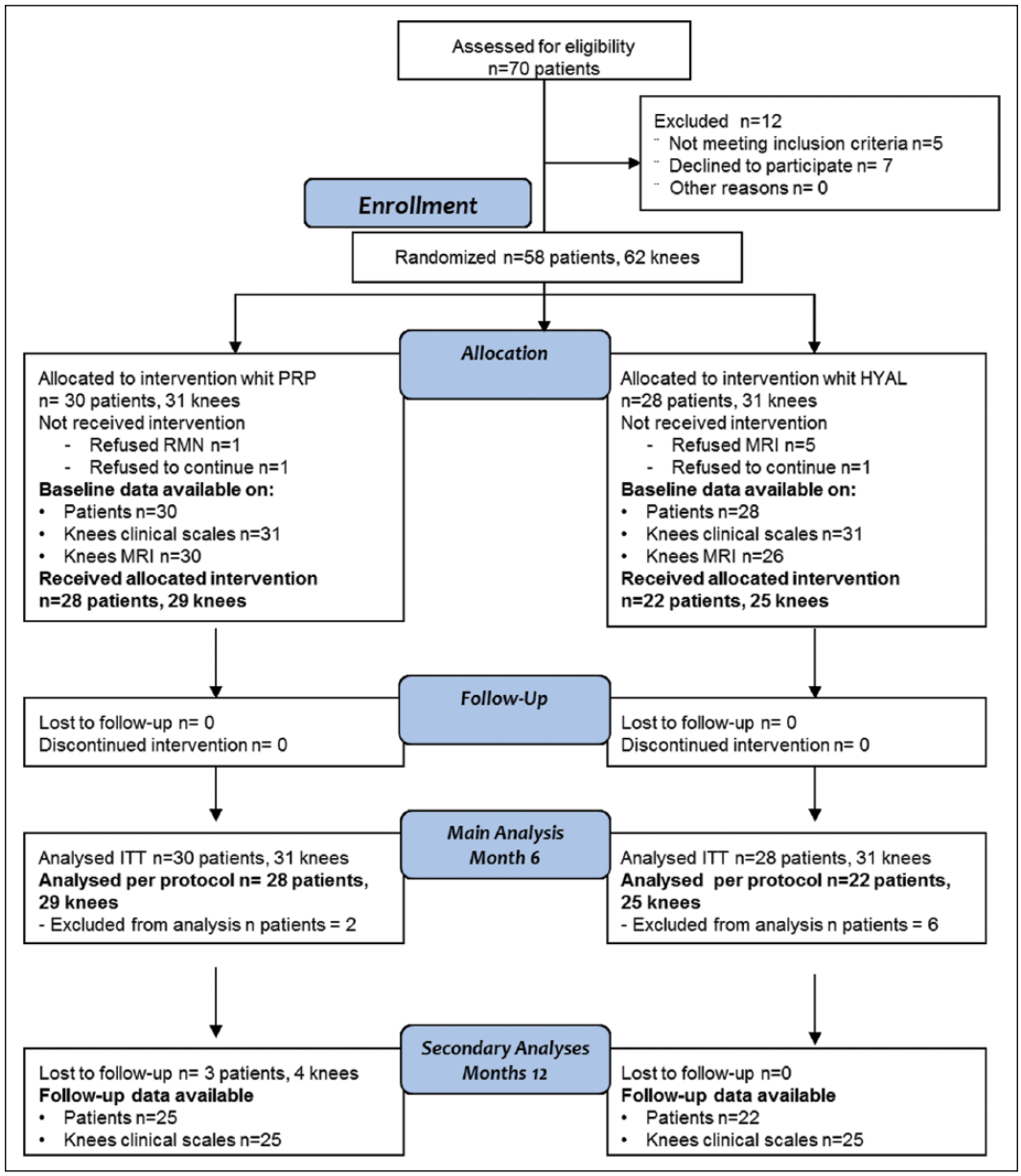


**Figure 1.** Patients' and knees' flowchart.
PRP: platelet-rich plasma; Hyal: hyaluronic acid; ITT: intention to treat; MRI: magnetic resonance imaging.

imaging. Besides, it reduces pain, improves function and ameliorates quality of life for at least one year.

In the past decade, many studies have been published on the intra-articular use of platelet products (usually platelet-rich plasma); advantages are the limited invasiveness of the procedures, the relatively low costs, the low infectious risk, thanks to the autologous blood, and the direct delivery on the poorly vascularized cartilage tissues. Preliminary in vitro studies showed effect of platelet-rich plasma on

**Table 2.** Primary outcome (improving at least one grade at the six-month magnetic resonance imaging)[12,21] comparison.

| Analysis | Category | Platelet lysate (knees $n = 31/29$) | % (with 95% CI) | Hyaluronic acid (knees $n = 31/25$) | % (with 95% CI) | *P*-value |
|---|---|---|---|---|---|---|
| Number of knees with missing primary outcome data | | 2 | | 6 | | |
| Intent-to-treat, missing = no improvement | Number of knees with >1 grade improvement | 14/31 | 25.8 (27.3–64.0) | 2/31 | 6.45 (0.8–21.4) | 0.002 |
| Intent-to-treat, missing = improvement | Number of knees with >1 grade improvement | 16/31 | 51.6 (33.0–69.8) | 8/31 | 25.8 (11.8–41.6) | 0.038 |
| Per protocol analysis | Number of knees with >1 grade improvement | 14/29 | 48.3 (29.4–67.5) | 2/25 | 8 (1.0–26.0) | 0.003 |

CI: confidence interval.

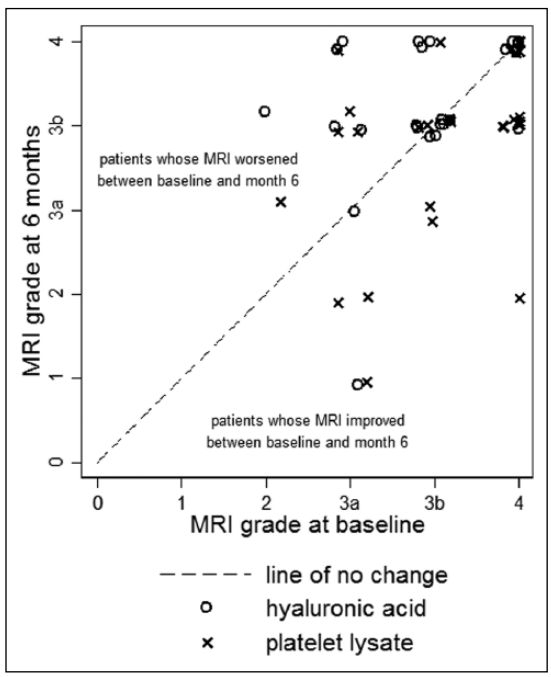


**Figure 2.** Change in magnetic resonance imaging grade from baseline to six months in the two groups.

fibroblasts, subsequently confirmed in animal studies.[22] It has been suggested that the favourable effect of platelet-rich plasma injections on symptoms does not exceed one year duration.[22,23] Among 50 patients treated with nine injections of platelet-rich plasma, no relevant improvement at MRI was seen at one year, despite improvement in functional and quality-of-life scales.[24] In our study, we found improvement in functional and quality-of-life indices in both groups: pain (in VAS and WOMAC) and articular range of movement. For some scales (Activities of Daily Living, WOMAC, Lysholm, Lequesne and AKSS), improvement was more evident (and statistically significantly so) in the activated platelet-rich plasma group and was still evident at the one year visit.[24,25]

Platelet-rich plasma also appear to have a role in the modulation of inflammation and in analgesia.[26] Therefore, repeat intra-articular platelet lysate injections can have a clinical role in modifying clinical evolution of osteoarthritis and delaying the need for surgery.

## *Research and theoretical implications*

Many important proteomic studies demonstrated that platelets contain hundreds of proteins able to induce numerous modifications for more than 1500 protein-based bioactive factors. The physiologic actions of many of these proteins have been clarified including growing factors, peptide hormones, chemoattractants

**Table 3.** Secondary outcomes comparison.

| Scale | Time | Hyaluronic acid ($n = 25$) | | | Platelet lysate ($n = 29$) | | | *P*-value |
|---|---|---|---|---|---|---|---|---|
| | | Median | IQR | Min-max | Median | IQR | Min-max | |
| VAS | Baseline | 6 | (5–7) | 3–8 | 6 | (5–7) | 0–8 | 0.78 |
| | 15 days | 2 | (1–4) | 0–7 | 1 | (0–4) | 0–7 | |
| | 6 months | 2 | (0–3) | 0–7 | 1 | (0–2) | 0–6 | |
| | 12 months | 1 | (0–3) | 0–4 | 0 | (0–2) | 0–6 | |
| WOMAC pain | Baseline | 7 | (4–9) | 3–13 | 4 | (3–6) | 1–13 | 0.91 |
| | 15 days | 4 | (2–5) | 0–8 | 1 | (1–3) | 0–9 | |
| | 6 months | 3 | (2–5) | 0–9 | 0 | (0–3) | 0–12 | |
| | 12 months | 3 | (1–5) | 0–11 | 0 | (0–1) | 0–10 | |
| WOMAC rigidity | Baseline | 3 | (1–3) | 0–5 | 2 | (0–4) | 0–6 | 0.58 |
| | 15 days | 1 | (0–2) | 0–4 | 1 | (0–1) | 0–6 | |
| | 6 months | 1 | (0–2) | 0–3 | 0 | (0–1) | 0–5 | |
| | 12 months | 0 | (0–2) | 0–5 | 0 | (0–1) | 0–4 | |
| WOMAC ADL | Baseline | 21 | (15–24) | 9–44 | 21 | (10–30) | 2–46 | 0.002 |
| | 15 days | 11 | (6–16) | 1–33 | 5 | (3–10) | 0–34 | |
| | 6 months | 11 | (7–20) | 0–24 | 4 | (2–9) | 0–33 | |
| | 12 months | 10 | (4–19) | 0–31 | 3 | (1–5) | 0–26 | |
| WOMAC total | Baseline | 29 | (25–35) | 16–61 | 27 | (13–38) | 4–59 | 0.16 |
| | 15 days | 17 | (8–22) | 2–45 | 9 | (4–13) | 0–44 | |
| | 6 months | 14 | (10–27) | 0–35 | 6 | (2–12) | 0–50 | |
| | 12 months | 14 | (6–28) | 0–43 | 3,5 | (1–8) | 0–40 | |
| AKSS | Baseline | 85 | (70–87) | 39–90 | 80 | (64–85) | 40–95 | 0.29 |
| | 15 days | 90 | (85–95) | 69–100 | 90 | (85–95) | 63–100 | |
| | 6 months | 90 | (85–95) | 70–100 | 95 | (90–100) | 58–100 | |
| | 12 months | 90 | (85–100) | 71–100 | 100 | (95–100) | 70–100 | |
| Lysholm | Baseline | 73 | (67–79) | 20–90 | 73 | (64–78) | 36–88 | 0.22 |
| | 15 days | 86 | (78–91) | 35–100 | 92 | (85–97) | 61–100 | |
| | 6 months | 83 | (77–90) | 68–100 | 94 | (85–99) | 63–100 | |
| | 12 months | 88 | (76–95) | 65–100 | 95 | (90–100) | 76–100 | |
| Tegner | Baseline | 3 | (2–3) | 1–5 | 3 | (3–4) | 2–7 | 0.63 |
| | 15 days | 3 | (3–4) | 1–5 | 4 | (3–4) | 2–7 | |
| | 6 months | 4 | (2–4) | 1–6 | 4 | (3–5) | 2–7 | |
| | 12 months | 4 | (3–4) | 2–5 | 5 | (3–6) | 2–6 | |
| Lequesne | Baseline | 7.5 | (6–9.5) | 3.5–13.5 | 8.5 | (6–12.5) | 2.5–15.5 | 0.04 |
| | 15 days | 4.5 | (3–6.5) | 0–10.5 | 4 | (1.5–5.5) | 0–11.5 | |
| | 6 months | 5 | (3–6) | 0–10 | 2 | (0.5–4) | 0–12 | |
| | 12 months | 3.5 | (1–5.5) | 0–11.5 | 1.5 | (0.5–3) | 0–9.5 | |
| Flexion | Baseline | 125 | (120–130) | 70–140 | 130 | (120–130) | 110–140 | 0.81 |
| | 15 days | 135 | (120–140) | 110–160 | 140 | (130–140) | 125–145 | |
| | 6 months | 140 | (130–140) | 105–150 | 140 | (135–140) | 120–145 | |
| | 12 months | 140 | (130–140) | 105–150 | 140 | (138–140) | 128–150 | |

IQR: interquartile range; VAS: visual analogue scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; ADL: activities of daily living; AKSS: American Knee Society Score.

for stem cells, macrophages, neutrophils, and a wide range of other proteins, such as fibrinogen and fibrin. In particular, fibrin could work as a temporary scaffold for stem or primary cell migration and differentiation and functions as a biological glue. Platelet dense granules also retain an antibacterial and antifungal effect together with the capacity of releasing adenoside diphosphate, adenoside triphosphate, dopamine, calcium ions and histamine that are active in tissue homeostasis and healing processes in concurrence with a broad spectrum of growth factors and other active molecules to the site of injury. Growth factors secreted by platelets include platelet-derived growth factor, epidermal growth factor, insulin-like growth factor, transforming growth factor-β1, vascular endothelial growth factor and hepatocyte growth factor. This wide variety of growth factors, acting in a synergistic way, definitely contributes to the broad spectrum of biological functions of platelet-rich plasma regarding enhancement of anabolism, bone remodeling, proliferation and angiogenesis. Especially, transforming growth factor-β1 is widely deemed one of the most important enhancers of matrix production, cell proliferation and chondrogenic differentiation. Hence, both the quantitative and qualitative components of platelet-rich plasma are substantial in mimicking or enhancing the natural processes of tissue repairing and facilitating the neoformation of cartilage.[27,28]

There is in vitro evidence that activated platelet-rich plasma is more rich in platelet-derived growth factor, epidermal growth factor and transforming growth factor-β than serum and that it stimulates growth of corneal epithelial cells.[29] This mechanism is triggered by the cooperation of platelet-derived growth factors (such as epidermal growth factor and platelet-derived growth factor A-B, promoting in particular cell proliferation) and the inhibitors of inflammation (e.g. interleukin-1 receptor antagonist and inhibitors of metalloproteinases).[29,30]

We did not find an association between platelet-derived growth factor concentration or number of platelets in peripheral blood and response. The high inter-patient variability in individual platelet-derived growth factors may explain this finding, since our study was insufficiently powered to detect this effect.[31] Also, our study confirms the good patient compliance with this technique and the safety of the three procedures.[22,32]

### *Limitations of the study*

We must acknowledge a number of limitations. The small sample size is the most obvious and precludes detection of statistically significant differences between groups in terms of pain and selected functional scales; however, we were able to detect difference in some important scales such as total WOMAC, AKSS and Lequesne.

Also, we could not determine the long-term radiological improvement. Longer-lasting effects, evident at MRI, might require a higher number of injections and a longer follow-up.[33]

More studies, larger and with a longer follow-up, are needed to standardize the procedures for platelet-rich plasma preparation, the number of necessary infiltrations, the interval between injections, the local anaesthesia, the long-term clinical effectiveness, the risk of short- and long-term adverse events and type and severity of the underlying osteoarthritis to be treated.[32]

**Clinical messages**

- Intra-articular-activated platelet-rich plasma reduces articular damage more than hyaluronic acid.
- It also reduces pain and improves patient's function and quality of life.
- It may have a role in delaying the need for surgery.
- Unresolved issues are the number of necessary infiltrations, the interval between injections, and others.

## Author contributions

The manuscript has been read and approved by all named authors and there are no other persons who satisfied the criteria for authorship.

## Contributors

C.L., G.D.N. and L.S. equally contributed to the authorship: designing the study, initiating it, monitoring progress, deciding on the analytic strategy and writing the paper itself. C.P. is the guarantor.

## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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## Studies involving humans or animals

In this study, animals are not involved.

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ORIGINAL ARTICLE

# Focused extracorporeal shock wave therapy combined with supervised eccentric training for supraspinatus calcific tendinopathy

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## ABSTRACT

BACKGROUND: Extracorporeal shockwave therapy (ESWT) is effective in reducing shoulder pain and improving function in calcific supraspinatus tendinopathy. Eccentric exercise has been introduced as an effective treatment choice for Achilles tendinopathy, but poor evidence exists about its role in the treatment of rotator cuff tendinopathy.
AIM: To investigate if adding a supervised eccentric training of the shoulder abductor muscles could improve the outcome of ESWT.
DESIGN: Pre-post intervention pilot study with matched control-group.
SETTING: Outpatient, University Hospital.
POPULATION: Twenty-two subjects affected by painful supraspinatus calcific tendinopathy.
METHODS: The study-group was assigned to receive focal ESWT (f-ESWT) plus a supervised eccentric training (SET) of the shoulder abductor muscles. The matched control-group received f-ESWT only. The post-treatment assessment at follow-up (T1) was performed nine weeks after the enrollment (T0). We assessed shoulder pain and function by the means of a numeric rating scale (p-NRS) and a DASH scale. As secondary outcome, we measured the isometric strength of the abductor muscles of the affected shoulder using a handheld dynamometer.
RESULTS: At T1, we recorded a significant decrease in pain ($P<0.001$) and an improvement in upper limb function ($P<0.001$) in both groups. However, we observed no statistical differences in favor of the study-group, in terms of p-NRS and DASH total score. A mild increase (+13% from baseline) of the maximum isometric abduction strength was noticed in the study group at T1.
CONCLUSIONS: Our findings did not support the hypothesis that adding a supervised eccentric training of the shoulder abductor muscles could improve the outcome (pain and function) of shock wave therapy.
CLINICAL REHABILITATION IMPACT: Our study confirmed that f-ESWT is effective in reducing shoulder pain and improving function in calcific supraspinatus tendinopathy. Adding a supervised eccentric training, focused on the abductor muscles, was useful to improve maximum isometric abduction strength, but appeared to give no advantage in the short-term outcome of shock wave therapy.

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**Key words:** Tendinopathy - Rotator cuff - Lithotripsy - Exercise.

Rotator cuff calcific tendinopathy, with particular involvement of the supraspinatus tendon, represents one of the most relevant causes of chronic shoulder pain between 30 and 60 years of age.[1, 2] Although the precise mechanism of injury leading to tendinopathy remains unknown, mechanical overloading is actually considered the major cause.[3, 4] The current gold standard in the therapy of tendinopathy of the rotator cuff remains a conservative approach.[5, 6] Efficacy on pain control of corticosteroid injection and non-steroidal

anti-inflammatory drugs is proven but usually limited in time.[6, 7] Among the remaining conservative treatments, extracorporeal shockwave therapy (ESWT) appeared to provide beneficial effects in various insertional tendinopathies and bone disorders.[8-10] ESWT is effective in reducing shoulder pain and improving function in patients affected by supraspinatus calcific tendinopathy.[8-20] Conversely, there is lack of scientific evidence confirming the efficacy of other physical therapies, such as ultrasound and laser therapy.[2, 5, 6] Supervised exercise has been shown to be as effective as surgery, in case of shoulder impingement syndrome, in reducing pain and improving function in both short and long-term perspective.[21, 22] In the last decade, eccentric exercise has been introduced as an effective treatment choice for Achilles tendinopathy,[23-26] but poor evidence exists about its role in the treatment of rotator cuff tendinopathy.[27, 28] Jonsson, Bernhardsson and Camargo reported, in subsequent non-randomized studies, an improvement in pain and function after eccentric trainings of the rotator cuff in chronic painful subjects with shoulder impingement syndrome.[29-31] In a randomized controlled study, Maenhout concluded that adding an eccentric exercise to a traditional rotator cuff training resulted in a higher gain in abduction isometric strength.[32] Until now, a single study analyzed the combined effect of shockwave therapy and eccentric exercise, but on Achilles tendinopathy only.[33] The same author previously demonstrated, in a randomized controlled trial on patients with calcific insertional Achilles tendinopathy, that shockwave therapy showed better clinical outcome than eccentric training.[34]

The aim of this pilot study is therefore to investigate if adding a supervised eccentric training of the shoulder abductor muscles could improve the outcome of focal ESWT (f-ESWT), with respect to shoulder pain, function and strength, in a population affected by supraspinatus calcific tendinopathy.

## Materials and methods

In a single-institution pre-post intervention study with matched control group, conducted from March 2013 to July 2015 in an outpatient rehabilitative setting, we collected data on subjects affected by monolateral painful supraspinatus tendinopathy. Inclusion criteria were adult age (18 to 65 years), duration of shoulder pain of six weeks or longer, clinical signs of sub-acromial impingement, normal passive glenohumeral range of movement and sonographic evidence of rotator cuff calcific tendinopathy, with the supraspinatus tendon lonely or predominantly affected. Exclusion criteria were general contraindication to ESWT (pacemaker, pregnancy, bleeding disorders or anticoagulant drug usage, cancer in the focal area), history of rheumatologic disease, previous fractures or surgery in the affected shoulder, full thickness tear of the rotator cuff tendons, frozen shoulder, clinical signs of cervical radiculopathy, corticosteroid injections or other conservative therapies (except pharmacological pain treatments) since the onset of the current pain episode.

The study-group was assigned to receive f-ESWT plus a supervised eccentric training (SET) of the shoulder abductor muscles; the control-group received f-ESWT only. The patients' allocation was made according to the criterion of age and sex homogeneity: for each case enrolled in the study-group, we enrolled a ±5-year-old control of the same gender in the matched control-group. At the beginning of the study, the first eligible patient was assigned to the study-group, then we progressively assigned the following eligible patients to the control-group, if "matchable" with one of the subjects already treated in the study-group, or to the study-group if not. A post-treatment evaluation (follow-up T1) was performed nine weeks after the first f-ESWT session (T0).

Participants signed their consent in accordance with the indications of the local ethical committee.

### *Procedures*

Before the enrollment, a specialized-PRM physician performed a clinical and an ultrasound examination of the affected shoulder in patients eligible for inclusion. The first f-ESWT session occurred one week after the enrolment. A device powered by a piezoelectric generator (PIEZOSON 100PLUS, Richard Wolf GmbH, Knittlingen, Germany) was used for f-ESWT. Participants underwent the treatment in sitting position, the affected shoulder lying on the side in internal rotation. At the beginning of each treatment session, the humeral enthesis of the supraspinatus tendon was targeted through a non-inline sonographic focusing, using a linear probe (7.5-

12 MHz) connected to an ultrasound scanner (MyLab™ Five, Esaote SpA, Genoa, Italy). All patients received 1700 pulses (frequency = 4 Hz) with an energy flux density of 0.15 mJ/mm$^2$ once a week for three consecutive weeks. We placed a coupling gel between the probes and the skin.

Both groups were asked for a pain therapy-free period (one week) before f-ESWT and to avoid pain-exacerbating activities throughout the study protocol. In case of transient severe pain exacerbations, we allowed the use of paracetamol (1000 to 2000 mg daily) during the treatment period, but we did not proceed to monitor its assumption by means of a journal. We asked the participants not to attend to any other treatment during the study protocol.

After the third f-ESWT session, participants assigned to the study-group started a six-week SET.

They attended four supervised physiotherapy sessions, twice a week for the first two weeks of training.

From the first session, they were educated to reproduce daily, at home, an eccentric exercise for the abductors muscles of the affected shoulder, using an elastic resistance band, as visualized in Figure 1. In particular, they were trained to perform the eccentric phase of the exercise at a speed of 5"/repetition, maintaining a full can modality (thumb up). We added stretching exercises for the anterior and posterior region of the shoulder before and after each training session. Each time the study-group participants returned to the clinic to perform the remaining three supervised sessions, a physiotherapist checked out the technique of execution, increasing the number of the series and the elastic resistance, in order to keep the intensity of the exercise through a mild pain (a value lower than 4 on a pain numeric rating scale). During the first two weeks of training, the exercise dosage provided for a progression from one to three series of 10 repetitions, with a pause of one minute between the series. During the residual four weeks, we asked them to continue the program daily, without supervision, at home.

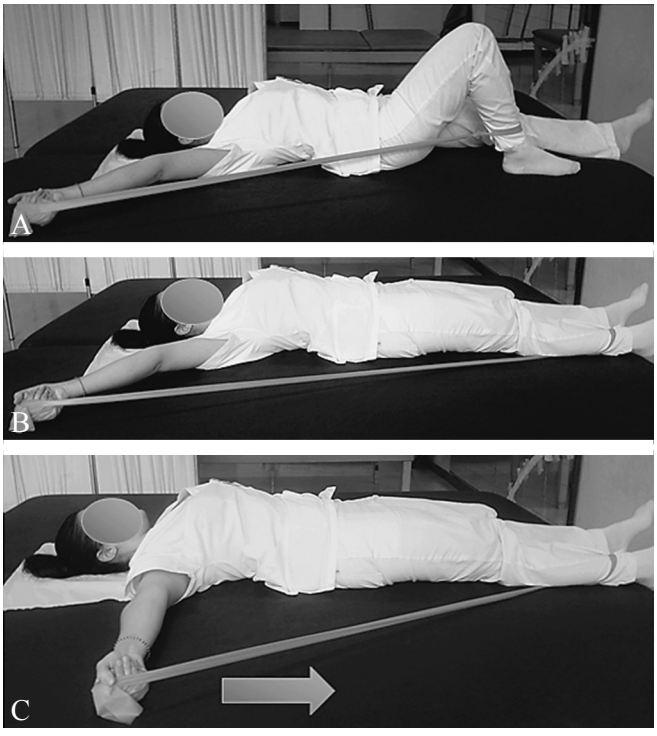


Figure 1.—Eccentric full-can abduction exercise: A) starting position; B) the elastic band is tensed up; C) eccentric phase.

*Outcome assessment*

At baseline, we recorded demographics, pain duration and localization (side) of the pathology.

At T0 and T1, we studied all participants for shoulder pain and function as primary outcome. We analyzed pain and function respectively by the means of a pain-on-movement numeric rating scale (p-NRS), ranging from zero ("no pain") to 10 ("the worst imaginable pain"), and a DASH scale, a self-administered questionnaire designed to measure functional performances and symptoms of the upper limb.[35-37] The DASH scale ranges from zero (no functional limitation) to 100 (complete shoulder inability). Each item of the DASH scale ranges from one (no difficulty) to five (unable to complete the task). We were particularly interested in two items, which reflect typically sub-acromial pain-exacerbating active movements: item number 6 ("place an object on a shelf above your head") and item number 15 ("put on a pullover sweater"). As secondary outcome, we measured the isometric strength of the abductor muscles of the affected shoulder, using a handheld dynamometer (TRACKER freedom wireless v.5 software, JTECH Medical). We performed the test, at T0 and at T1 follow-up, with patients in sitting position, the upper limb at 40° of shoulder abduction from the trunk, in neutral humeral rotation and with the elbow extended. During the test,

we used standardized verbal instructions to achieve the maximal isometric effort, as the examiner pushed down the affected limb with the dynamometer at the forearm level. The examiner repeated each measurement twice and registered the maximum value of isometric strength expressed (Isom Fmax), measured in newtons (N).

### *Statistical analysis*

The Shapiro-Wilk test was used to analyze the normal distribution of quantitative variables; the results were expressed as mean values and standard deviation (SD) as they were all normally distributed; qualitative variables were summarized as counts and percentages. *t*-test for paired data was used to analyze pre-post therapy differences and *t*-test for independent data for comparisons between groups.

A regression model for repeated measures was use to adjust for the p-NRS in the comparisons of Isom Fmax at T0. A $P<0.05$ was considered statistically significant and all tests were two-sided. Data analysis was performed with STATA statistical package (release 14, 2015; Stata Corporation, College Station, TX, USA).

## Results

Twenty-six patients fulfilled the inclusion criteria during the observation period. We excluded two of them because of a recent corticosteroid injection treatment; two further patients refused to participate. Finally, we enrolled 22 participants. Data about basic demographics, pain duration and localization (side) of the pathology are shown in Table I. At baseline, we observed no statistical differences between groups in terms of side affected (P=0.39) and duration of pain (P=0.58). No patient was lost at 9-week follow-up.

All the participants felt the f-ESWT unpleasant but tolerable. No patients stopped the therapy because of the pain. We recorded no local side effect; one patient referred a mild and transient dizziness at the end of the third session of treatment. The eccentric loading was well tolerated by the patients of the study-group, who reported mild shoulder pain during exercise, always promptly disappearing at rest.

TABLE I.—*General assessment data and outcome measures at baseline (T0) and at follow-up (T1).*

| Variables | Control group | Study group | P value |
|---|---|---|---|
| Sample | 11 | 11 | |
| Sex female/male | 7/4 | 7/4 | 1 |
| Mean age, years | 49.5±8.6 | 50.3±9.1 | 0.8309 |
| Pain onset, months | 6.2±6.7 | 4.8±3.3 | 0.5724 |
| Painful side, right/left | 5/6 | 8/3 | 0.387 |
| p-NRS at T0 | 6.4±1.6 | 5.3±1.5 | 0.113 |
| p-NRS at T1 | 2.9±2.7 | 1.4±1.1 | 0.1014 |
| DASH total score at T0 | 39.1±14.6 | 34.8±14.6 | 0.5005 |
| DASH total score at T1 | 18.8±16.8 | 16.1±9.7 | 0.6440 |
| DASH item6 at T0 | 3.5±0.7 | 3.2±1 | 0.4826 |
| DASH item6 at T1 | 2±1 | 2.1±0.6 | 0.7735 |
| DASH item15 at T0 | 3±0.9 | 2.5±1 | 0.3360 |
| DASH item15 at T1 | 2±1.3 | 1.7±0.7 | 0.5109 |
| Isom $F_{max}$ at T0, newtons | 125.6±37 | 101.5±44 | 0.2000 |
| Isom $F_{max}$ at T1, newtons | 129.4±25.1 | 116.7±51.5 | 0.4765 |

Data is presented as mean ± SD.
p-NRS: pain Numeric Rating Scale; DASH: Disability of the Arm, Shoulder and Hand scale; Isom $F_{max}$: maximum value of isometric abduction strength.

### *Primary outcome: pain and function*

Group data for all outcome measures at T0 and T1 are reported in Table I. We observed no statistical differences between groups in terms of p-NRS (P=0.11) and DASH total score (P=0.5) at baseline. Comparisons between groups (expressed in delta values T0–T1), are shown in Table II and in Figure 2.

At follow-up, we recorded a statistically significant decrease in pain-NRS ($P<0.001$) and an improvement in upper limb function ($P<0.001$), measured by DASH total score, in both groups (Table I). However, we observed no statistical differences in favor of the study-group, in terms of p-NRS (P=0.65) and DASH total score (P=0.84), as visualized in Table II and Figure 2. DASH item 6 and 15 followed the same trend as DASH total score (Tables I, II).

TABLE II.—*Outcome measures: pre-post treatment differences (T0-T1).*

| Variable (T0–T1 difference) | Control group | Study group | P values |
|---|---|---|---|
| p-NRS | 3.45±2.07 | 3.82±1.6 | 0.6496 |
| DASH total score | 20.32±23.01 | 18.79±9.97 | 0.8425 |
| DASH item6 | 1.4±1.17 | 1.11±0.78 | 0.5413 |
| DASH item15 | 1.3±1.42 | 0.89±0.6 | 0.4318 |
| Isom $F_{max}$, newtons | -3.82±29.99 | -15.11±18.97 | 0.3409 |

p-NRS: pain Numeric Rating Scale; DASH: Disability of the Arm, Shoulder and Hand scale; Isom $F_{max}$: maximum value of isometric abduction strength.

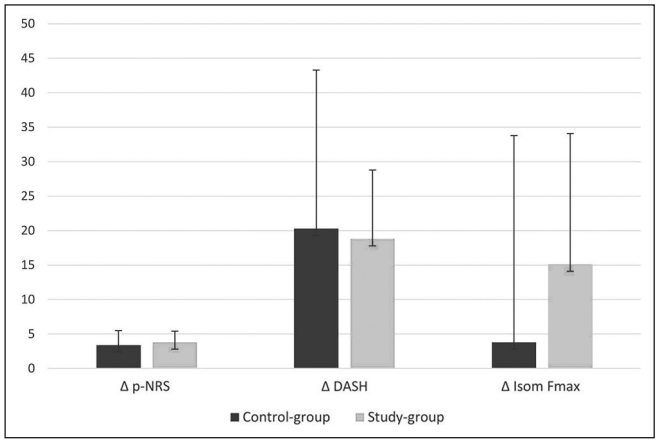


Figure 2.—Comparison between groups expressed in ΔT0-T1. No differences between groups were found in the statistical analysis. An increase of 13% from the baseline maximum isometric abduction strength was observed in the study group at T1 (P=0.34).

*Secondary outcome: strength*

Values of maximum isometric strength in shoulder abduction are expressed in Table I.

At T0, the study-group expressed slightly lower values of maximum isometric strength in the affected shoulder than the control-group, but this difference was not statistically significant (P=0.2). The regression model excluded that such baseline difference might have depended on the p-NRS values. A mild increase of maximum isometric strength in shoulder abduction at 40° (+13% from baseline) was noticed in the SET-performing group at T1, however not statistically significant (Figure 2).

## Discussion

Our findings did not support the hypothesis that adding a supervised eccentric training of the shoulder abductor muscles could improve the outcome (pain and function) of f-ESWT in the treatment of calcific supraspinatus tendinopathy. Our study confirmed that f-ESWT is effective in reducing shoulder pain and improving function, but we observed no statistical differences in favor of the SET-performing group after treatment. Nevertheless, we found a mild but not significant increase (+13% from baseline) in the maximum isometric abduction strength after the SET.

Our findings should be read to the light of the following pending arguments. First, few studies have been published about the effectiveness of an eccentric training program for rotator cuff tendinopathy, so poor evidence exists about the use of this type of exercise. In most cases, those studies enrolled subjects affected by sub-acromial impingement syndrome, excluding patients with tendon tears, but not clearly defining the cause of sub-acromial pain.[27-37] Second, the way of action of both shockwaves therapy [38-40] and eccentric training [28, 41, 42] is based on a mechano-transduction pathway but the precise biological mechanism of action is not yet fully understood.[40] Third, even in presence of a potential rationale of a combined use of shockwaves and eccentric training, a single study analyzed the clinical outcome of such a strategy. In 2009, Rompe reported better results (therapeutic success in 82% of the cases) of a combined use of eccentric training plus radial ESWT *versus* eccentric loading alone (56%) in the treatment of mid-portion Achilles tendinopathy.[33] More recently, Kvalvaag proposed a new study protocol to investigate the efficacy of a combined use of radial ESWT and supervised exercises (including eccentric exercises) in patients affected by sub-acromial shoulder pain,[43] but further studies are needed to confirm the efficacy of eccentric exercise in improving the outcome of ESWT in this field.

With regard to the exercise protocol, we chose a supervised eccentric exercise for shoulder abductor muscles only, in order to keep the training simple and home reproducible and to improve patients' compliance. We selected the supine position in order to obtain a better scapulothoracic joint stabilization and a better upper-spine muscles relaxation than the upright position, relying on the fact that the elastic band and the full-can modality would have reduced the impingement-effect linked to the supine position. The option of a full-can modality of exercise was justified by the fact that the supraspinatus activity is optimized in this position, with reduced deltoid recruitment.[44, 45] There is a lack of evidence regarding those factors which might influence the outcome of an eccentric training, in particular about the duration. Previous works are heterogeneous in terms of dosage, duration (6 to 12 weeks) and modality of exercise: Jonsson focused on a supraspinatus-deltoid eccentric strengthening lasting 12 weeks,[29] Bernhardsson on a supraspinatus plus infraspinatus 12 weeks eccentric training,[30] Camargo proposed a 6 weeks eccentric isokinetic training for shoulder abductors, reporting a

significant decrease in pain and disability.[31] A single randomized controlled trial by Maenhout pointed-out that adding an eccentric exercise to a traditional rotator cuff training resulted in a higher gain (15%) in abduction isometric strength, but was not more effective in decreasing pain and improving function after 12 weeks of training.[32] In comparison to the literature, the shorter duration (six weeks) of our exercise protocol should not have influenced the outcome, since Maenhout reported a significant increase in isometric abduction strength at the 6th week of training, but not from the 6th to the 12th week. He also reported that most of the clinical improvement also took place during the first six weeks of training. In fact, the performance of our study-group at follow up is in line with the results reported by Maenhout.[32] The lack of a longer follow-up, instead, could have negatively influenced our understanding of the SET outcome, masking the longer benefits of this type of exercise, since the supposed biological effects usually require a longer period to consolidate.[28]

Finally, it might be interesting to compare the maximum isometric strength values of our sample to the healthy population. In 2009, a Danish group of authors reported a set of reference measures for maximal isometric muscle strength of the major body muscles. If we try to approximate a comparison, taking into account the technical differences in measurement and adjusting for the lever arm, the maximum isometric abduction strength values of our population at baseline appear to be about in line with those of the youngest group of Danneskiold-Samsøe.[46]

### *Limitations of the study*

The present study has several limitations. First, the small number of patients enrolled. Given the small size and the not randomized design of this pilot trial, the present falls under the "hypothesis-concerning" type of study. Second, as mentioned earlier, the lack of a longer follow-up prevented further comparisons with the previously published literature and the evaluation of the impact of our exercise program on the medium and long-term. However, one of the main problem in the conservative management of tendinopathy is the long duration of the treatments, so that most patients are usually poorly compliant. For such reason, and expressing an everyday practice need, we focused our approach on treating and evaluating our sample in a short-term outcome. Third, the investigators could not be blinded to the group assignment, but the influence of their expectations about the outcome was probably marginal, since both groups showed marked improvement over time.

## Conclusions

f-ESWT is effective in reducing shoulder pain and improving function of patients affected by calcific supraspinatus tendinopathy. Adding a supervised eccentric training, focused on the abductor muscles, brought to a mild improvement in maximum isometric abduction strength, but appeared to give no advantage in the short-term outcome (pain and function) of shockwave therapy.

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*Conflicts of interest.*—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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# Significance of serum Myostatin in hemodialysis patients

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## Abstract

**Background:** Malnutrition and muscle wasting are common in haemodialysis (HD) patients. Their pathogenesis is complex and involves many molecules including Myostatin (Mstn), which acts as a negative regulator of skeletal muscle. The characterisation of Mstn as a biomarker of malnutrition could be useful in the prevention and management of this condition. Previous studies have reported no conclusive results on the actual relationship between serum Mstn and wasting and malnutrition. So, in this study, we evaluated Mstn profile in a cohort of regular HD patients.

**Methods:** We performed a cross-sectional study, enrolling 37 patients undergoing bicarbonate-HD (BHD) or haemodiafiltration (HDF) at least for six months. 20 sex-matched healthy subjects comprised the control group. Mstn serum levels were evaluated by ELISA before and after HD. We collected clinical and biochemical data, evaluated insulin resistance, body composition, malnutrition [by Malnutrition Inflammation Score (MIS)] and tested muscle function (by hand-grip strength, six-minute walking test and a questionnaire on fatigue).

**Results:** Mstn levels were not significantly different between HD patients and controls (4.7 ± 2.8 vs 4.5 ± 1.3 ng/ml). In addition, while a decrease in Mstn was observed after HD treatment, there were no differences between BHD and HDF. In whole group of HD patients Mstn was positively correlated with muscle mass ($r = 0.82$, $p < 0.001$) and inversely correlated with age ($r = -0.63$, $p < 0.01$) and MIS ($r = -0.39$, $p = 0.01$). No correlations were found between Mstn and insulin resistance, such as between Mstn levels and parameters of muscle strength and fatigue. In multivariate analysis, Mstn resulted inversely correlated with fat body content ($\beta = -1.055$, $p = 0.002$).

**Conclusions:** Circulating Mstn is related to muscle mass and nutritional status in HD patients, suggesting that it may have a role in the regulation of skeletal muscle and metabolic processes. However, also considering the lack of difference of serum Mstn between healthy controls and HD patients and the absence of correlations with muscle function tests, our findings do not support the use of circulating Mstn as a biomarker of muscle wasting and malnutrition in HD.

**Keywords:** Hemodialysis, Myostatin, Malnutrition, Muscle wasting, Bioimpedance analysis

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## Background

Patients suffering from chronic kidney disease (CKD), mainly those undergoing hemodialysis (HD), often present malnutrition and muscle wasting, which directly correlate with morbidity and mortality [1]. Aetiology and pathophysiology of these conditions are complex and multifactorial, involving physical inactivity, insulin resistance, nutritional and hormonal changes and loss of muscle fibres [2]. Due to the relevant clinical impact of malnutrition and wasting, many attempts have been made to find a comprehensive definition of these conditions, in order to standardize diagnostic and therapeutic approaches. The different definitions took into consideration the levels of putative serum malnutrition markers (such as albumin and prealbumin), body mass index (BMI), the analysis of body composition and the evaluation of nutritional status by specific questionnaires (such as Subjective Global Assessment, SGA) [3]. However, while it is clear that an adequate evaluation of nutritional status requires a multistep approach, on the other hand the individuation of feasible and reproducible markers, allowing early diagnosis and monitoring of malnutrition and muscle wasting, is potentially useful [4].

Recently, the study of molecular and cellular mechanisms involved in the regulation of energy and muscular homeostasis has gained much interest. Myokines are molecules produced and released by skeletal muscle cells with systemic and paracrine actions, related to the activation of intracellular signalling pathways. These molecules, which include Myostatin, Irisin and IL-6, may have positive or negative effects on muscle growth and regulate relevant processes, such as increase fat oxidation, insulin sensitivity and inflammation [5].

The Growth Differentiation Factor (GDF)-8/Myostatin (Mstn) is a member of the Transforming Growth Factor (TGF)-β superfamily, primarily expressed in skeletal muscle cells and found also in other different cells and tissues, such as cardiomyocytes, macrophages and vessels. It is synthesized as a 376 amino acid pre-propeptide, then processed into an inhibitory propeptide of 242 amino acids and an active peptide of 110 amino acids [6].

Mstn exerts its effects in both autocrine and paracrine ways by binding a cell-bound Activin type II receptor 2B (ActRIIB) which, assembling itself with ALK4 or ALK5, leads to the activation of intracellular signalling pathways, including Smad 2/3 and Akt [7].

In skeletal muscle, Mstn limits muscle growth and promotes protein breakdown and its inhibitory effects have been described in both experimental models and clinical settings, with several studies demonstrating its increased expression in atrophic muscle and chronic diseases [8].

Although its action on skeletal muscle candidates serum Mstn as a potential biomarker for muscle wasting, the relationship between serum Mstn and skeletal muscle mass is still unclear.

Indeed, while the muscle-wasting effects of tissue myostatin are well established, many studies investigating serum Mstn in different disease conditions gave conflicting results, showing that Mstn may be both directly or inversely related to muscle mass or muscle wasting [9, 10].

In CKD patients an up-regulation of Mstn gene expression in skeletal muscle has been found, which was related to IL-6 expression, suggesting a link between Mstn and microinflammation [11]. Moreover, it has also been recently described that uremic toxins may accelerate muscle atrophy, by inducing Mstn expression [12]. However, only few studies have been focused on the evaluation of serum Mstn in CKD patients [13, 14].

Therefore, in this study we tried to characterize the profile of circulating Mstn and investigate its potentiality as a biomarker of malnutrition and muscle wasting in HD patients.

## Methods

### Study design

Adult (> 18 years) maintenance HD patients who had undergone HD for at least 6 months were enrolled in a cross-sectional. We excluded patients with: i) acute diseases, such as infections or immunological disorders, ii) immunosuppressive therapy, iii) history of transplantation or cancer. The control group was constituted by sex-matched healthy subjects.

We enrolled patients undergoing standard low-flux bicarbonate hemodialysis (BHD) or on-line hemodiafiltration (HDF) in a 2:1 ratio. BHD was performed with cellulose-based membranes using a blood flow rate of 300–350 mL/min (DICEA®,©Baxter International, IL, USA), while HDF was performed with high-flux membranes using a convective volume of 25–30% (FX100 High –Flux®,©Fresenius Medical Bad Hamburg, Germany).

For each patient we collected: i) clinical data, including age, dialysis modality, dialysis vintage and body mass index (BMI), and ii) biochemical data, such as pre-dialysis potassium, phosphate, transferrin, albumin, and C-reactive protein (CRP) serum levels. McAuley index (McA) = exp. [2.63–0.28 ln (insulin in mU/l) – 0.31ln (triglycerides in mmol/l)] was used to define insulin resistance (IR), considering a diagnostic cut-off point of ≤5.8 [15]. Serum Mstn level was tested by ELISA (Quantikine; R&D Systems, Minneapolis, MN, USA; detection limit 5.3 pg/ml), at the beginning and at the end of the hemodialysis session.

The study was performed according to the Declaration of Helsinki and was approved by the local Ethics Committee (protocol n. 9358/2015). All participants provided written informed consent before the enrollment.

### Body composition and nutritional evaluations

Body composition was studied by Body Composition Monitor (BCM, FMC, Bad Homburg, Germany). Measurements were taken before the HD treatment with the patient supine; electrodes were attached to the hand and foot on the same side of the body. As previously reported, a 3-compartment model of the body composition was applied. This model provides data on overhydration (OH), lean tissue index (LTI) and fat tissue index (FTI), normalized to height squared [16, 17].

Malnutrition-Inflammation Score (MIS) was used to assess nutritional status. It consists of ten items: modification in end-dialysis dry weight, dietary intake, comorbidities, functional capacity, gastrointestinal symptoms, BMI, loss of subcutaneous fat, decreased fat stores or/and signs of sarcopenia (according to SGA), serum albumin and total iron-binding capacity. Each item can present four levels of severity, from 0 (normal) to 3 (severely abnormal). Therefore, the MIS score can range from 0 to 30, with a higher score reflecting greater malnutrition and inflammation severity [18]. A score of 5 or above was considered to be indicative of malnutrition.

### Muscle function tests

All functional assessments were conducted by two trained assessors before the beginning of the HD session, in a quiet environment, using a standardized protocol, and included the dynamometer handgrip strength (HGS), the 6 min walking test (6MWT) and the Fatigue Severity Scale (FSS) [19]. The HGS was measured on the non-fistula arm using a Jamar hand dynamometer, considering the highest HGS value after three trials (with a one-minute pause between trials) [20].

6MWT was performed according to the American Thoracic Society guidelines. The respondents were asked to walk for 6 min along a 30 m corridor under medical supervision, at the normal pace they used daily. Test results consisted of the total covered distance, measured in m (with an accuracy of 1 m) [21].

Finally, muscular fatigue was assessed by FSS, a 9-item self-report questionnaire where each item is scored 1–7. The total score range from 9 to 63 and a score > 36 was considered pathological.

### Statistical analysis

Data are presented as mean ± standard deviation (SD) or interquartile ranges (IQR), if not normally distributed (as evaluated by Shapiro Test).

Analysis of variance (ANOVA), Student t-test or non-parametric Mann-Whitney test, were used to assess the differences among control group and HD patients. Spearman-Rho was used to assess the correlations between Mstn and clinical and laboratory variables, while logistic regression models were used to analyze the associations (Stata 13.1, Stata Corporation, College Station, Texas, United States). A 2-tailed $P$ value < 0.05 was considered statistically significant.

## Results

### Patient characteristics

We enrolled 37 HD patients (69.6 ± 15 years, 14 females) with a dialysis vintage of 35 (19.5–48) months. At the time of enrollment, 24 patients (65%) were undergoing thrice-weekly 4-h BHD, while 13 patients (35%) HDF.

32 patients (86%) were hypertensive, 12 patients (32%) were diabetic and 12 patients (32%) were active smokers. The main underlying nephropathies included glomerulonephritis, nephroangiosclerosis, diabetic nephropathy and adult dominant polycystic kidney disease.

Mean BMI was 26.4 ± 4.2 kg/m$^2$, while mean predialytic potassium, albumin and CRP were 4.6 ± 0.7 mEq/l, 32 ± 4 (3.2 ± 0.4) g/dl and 0.76 (0.25–1.2) mg/dl, respectively. Mean McAuley index was 5.6 ± 2. Considering a cut-off of ≤5.8, 23 patients (62%) resulted insulin-resistant.

20 healthy subjects (48.5 ± 10 years, $p < 0.01$ vs HD, 8 females), with normal renal function (creatinine 78.2 ± 16 μmol/L) and mean BMI of 27 ± 2 kg/m2, constituted the control I group.

Whole patient characteristics are shown in Table 1.

### Myostatin profile

There was no significant difference in serum Mstn levels between pre-dialysis HD and Control groups (4.7 ± 2.8 vs 4.4 ± 1.3 ng/ml, $p = 0.8$). Moreover, in the HD group post-dialysis Mstn levels resulted significantly lower than pre-dialysis ones (4.2 ± 2.6 ng/ml, $p = 0.02$). Finally, taking into consideration the different dialytic modalities, we found no differences in Mstn levels, comparing patients undergoing BHD or HDF (4.7 ± 2.8 vs 4.6 ± 3 ng/ml) (Fig. 1).

### Nutritional parameters and functional tests

As recorded by BCM, mean LTI and FTI were 12.3 ± 2.9 and 14 ± 5.9 kg/m2, respectively. There were no significant differences between female and male patients.

Mean MIS score was 14 ± 3. Considering a MIS cut-off ≥5, we demonstrated the presence of malnutrition in all the evaluated HD patients.

All participants completed the functional assessment. Mean HGS was 25.1 ± 9 kg, but it was significantly lower in women than in men (19.8 ± 5.9 vs 27.7 ± 9.3 kg, $p < 0.05$). The average distance achieved in the 6MWT was 365 ± 79 m.

Finally, mean FSS was 45 ± 11, presenting a clear pathological value (i.e. > 36) in 31 patients (83%) (Table 2).

**Table 1** Patient characteristics at the time of clinical observation

| | Total population |
|---|---|
| N | 37 |
| Gender (M/F) | 23/14 |
| Age, (years) | 69.6 ± 15 |
| BMI, (kg/m$^2$) | 26.4 ± 4.2 |
| Diabetes, n (%) | 12 (32) |
| Time on dialysis, months (IQR) | 35 (19.5–48) |
| Type of dialysis, n (%) | |
| BHD, n (%) | 24 (65) |
| HDF, n (%) | 13 (35) |
| Serum potassium (mEq/L) | 4.6 ± 0.7 |
| Serum albumin (g/L) | 32 ± 0.4 |
| Prealbumin (g/L) | 0.3 ± 0.08 |
| Total cholesterol (mmol/L) | 3.6 ± 0.9 |
| Triglycerides (mmol/L) | 1.8 ± 0.8 |
| Phosphate (mmol/L) | 1.6 ± 0.5 |
| McAuley index | 5.6 ± 2 |
| CRP (mg/dl), IQR | 0.76 (0.25–1.2) |
| Transferrin (g/L) | 1.7 ± 0.3 |
| spKT/V | 1.66 ± 0.3 |

All values were determined in predialysis
Abbreviations: Body mass index (BMI), Bicarbonate-hemodialysis (BHD); Hemodiafiltration (HDF), C-reactive protein (CRP), standard pool KT/V (spKT/V)

## Correlations

Correlation analysis showed a direct association between pre-dialysis Mstn and LTI, albumin and phosphate serum levels (Fig. 2), whereas there was a significant inverse association with age, BMI, FTI and MIS. Moreover, MIS resulted inversely correlated with serum albumin levels and LTI, while was directly correlated with age, CRP levels, OH state (r = 0.44) and fatigue, expressed as FSS (r = 0.37, $p = 0.02$) (Table 3). McAuley index, defining insulin resistance (i.e. lower values correspond to increased risk of IR), was inversely correlated with BMI and FTI and directly related to HD vintage and OH. HGS was directly correlated with muscle mass, expressed as LTI (r = 0.41, $p = 0.01$), and inversely correlated with age (r = − 0.35, $p = 0.04$).

Finally, in multivariate analysis, after adjustment for age, sex and HD vintage, Mstn resulted inversely associated with FTI (β = − 1.055, $p = 0.002$).

## Discussion

In this study, we tried to define the meaning of serum Mstn in HD patients.

First, we evaluated the circulating levels of Mstn and the potential effect of dialytic treatment on these levels, taking into consideration different dialysis techniques (BHD vs HDF). We found no differences in Mstn levels between HD patients and healthy control, while there was a significant slight decrease of Mstn after a single

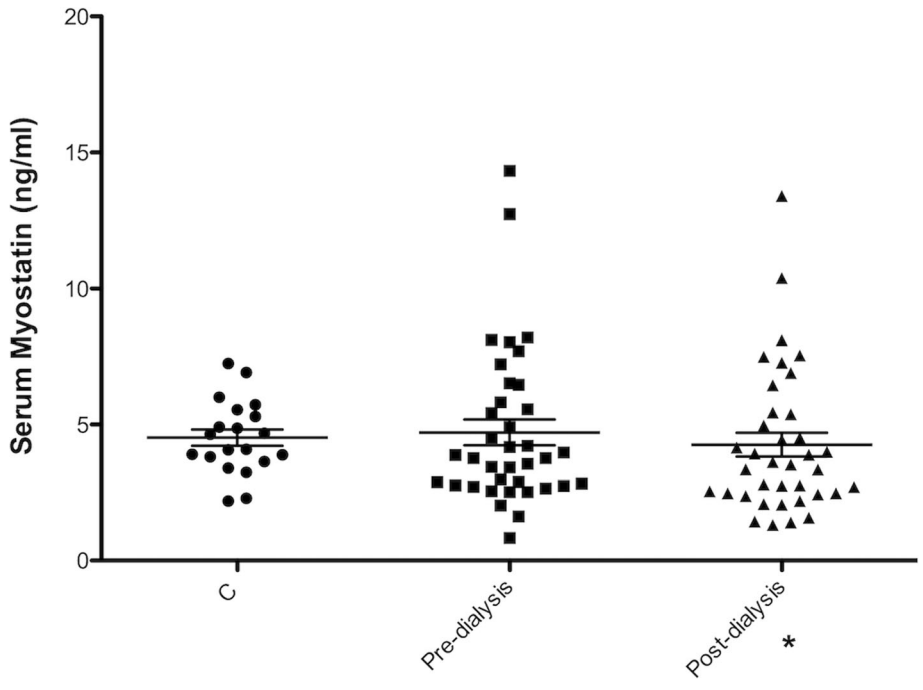


**Fig. 1** Serum Myostatin levels in HD patients. There were not significant differences in serum myostatin levels between healthy control subjects (C) and patients undergoing hemodialysis. Post-dialysis there was a significant decrease in Myostatin levels compared with pre-dialysis values. * $p < 0.05$

**Table 2** Body composition and muscle function tests at the time of clinical observation

| | Total population |
|---|---|
| N | 37 |
| Serum Myostatin (ng/ml) | 4.7 ± 2.8 |
| LTI, (kg/m$^2$) | 12.3 ± 2.9 |
| FTI, (kg/m$^2$) | 14 ± 5.9 |
| OH (L), IQRs | 0.5 (−0.9_1.2) |
| MIS | 14 ± 3 |
| HGS (kg) | 25.1 ± 9 |
| Male (n.24) | 27.7 ± 9.3 |
| Female (n.13) | 19.8 ± 5.9* |
| 6MWT (m) | 365 ± 79 |
| FSS | 45 ± 11 |

All values were determined in predialysis. * $p < 0.05$ vs males
Abbreviations: Lean Tissue Index (LTI), Fat tissue index (FTI), Body mass index (BMI), Overhydration (OH), Malnutrition Inflammation Score (MIS), Hand-grip strength (HGS), 6-min walking test (6MWT), Fatigue Severity Scale (FSS)

HD session, confirming our previous data of a potential modulation of serum Mstn by HD treatment [22]. However, in contrast with other reports, we did not observe significant differences in Mstn levels between BHD and HDF [14, 22].

This finding could be explained by many factors, including the diverse assays used to measure circulating Mstn, the different study design (crossover vs observational) and the small number of patients enrolled in these studies that may have not allowed to discriminate little differences between the two HD modalities.

Furthermore, basing on the known inhibitory effects of Mstn on skeletal muscle growth, we investigated the hypothetical use of serum Mstn level as a biomarker for muscle wasting, a very common condition in HD patients, significantly related to relevant clinical consequences.

Therefore, we studied circulating Mstn in relation to nutritional and metabolic parameters and muscle function tests. Interestingly, we found that in HD patients serum Mstn resulted directly correlated with muscle mass, evaluated by BIA. Coherently, circulating Mstn resulted inversely correlated with BMI, fat body content and age, indicating that obese and older patients with low muscle mass present low circulating Mstn levels. This data was also reinforced by the evidence of direct correlation of Mstn with albumin and phosphate levels, often used as markers of good nutritional status, and its inverse correlation with malnutrition, evaluated by MIS.

All these findings are in apparent contradiction with those reported in skeletal muscle and suggest that circulating Mstn reflects muscle mass content rather than muscle wasting. On the other hand, this data is not so surprising, since the actual relationship between serum Mstn and skeletal muscle mass in humans remains controversial. Indeed, while there is evidence of an inverse correlation between serum Mstn and skeletal muscle mass in elderly and patients affected by chronic diseases, it has been also reported that low serum Mstn levels are associated with low skeletal muscle mass in in heart

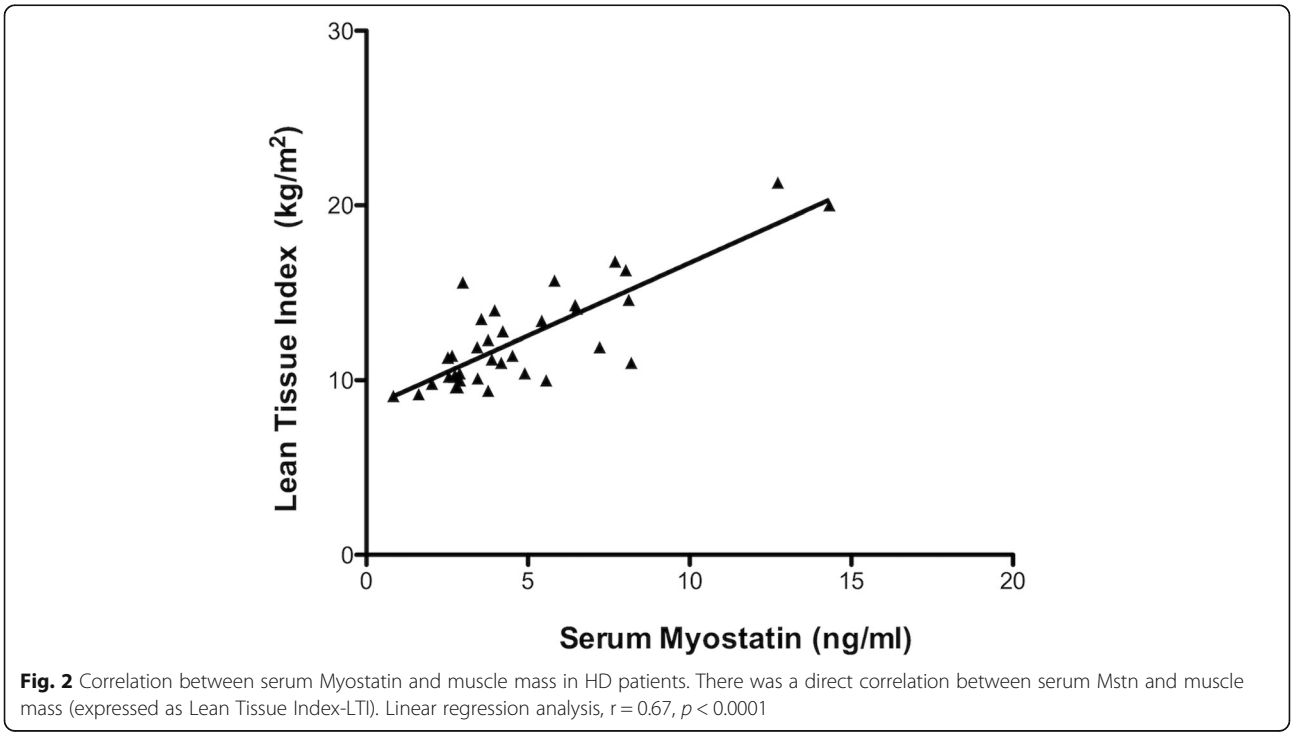


**Fig. 2** Correlation between serum Myostatin and muscle mass in HD patients. There was a direct correlation between serum Mstn and muscle mass (expressed as Lean Tissue Index-LTI). Linear regression analysis, r = 0.67, $p < 0.0001$

**Table 3** Correlations among Myostatin serum levels, nutritional and functional parameters in HD patients

| *N* = 37 | Age | HD-age | MSTN | Phosphate | BMI | LTI | FTI | CRP | Albumin | McA | MIS |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | 1 | | | | | | | | | | |
| HD-age | 0.12 | 1 | | | | | | | | | |
| MSTN | −0.63§ | 0.01 | 1 | | | | | | | | |
| Phosphate | − 0.44+ | − 0.08 | 0.4* | 1 | | | | | | | |
| BMI | 0.06 | −0.09 | − 0.4* | − 0.06 | 1 | | | | | | |
| LTI | −0.68 § | 0.143 | 0.82 § | 0.38* | −0.45 | 1 | | | | | |
| FTI | 0.28 | −0.2 | −0.65 § | − 0.18 | − 0.18§ | −0.7 § | 1 | | | | |
| CRP | 0.27 | 0.17 | −0.19 | −0.12 | 0.05 | −0.17 | −0.06 | 1 | | | |
| Albumin | −0.09 | −0.04 | 0.35* | 0.02 | 0.14 | 0.3 | −0.01 | −0.07 | 1 | | |
| McA | 0.19 | 0.43+ | 0.06 | −0.09 | −0.54+ | 0.18 | −0.45+ | − 0.006 | −0.18 | 1 | |
| MIS | 0.47+ | −0.06 | −0.39* | − 0.04 | −0.29 | − 0.44+ | −0.02 | 0.37* | −0.43* | 0.12 | 1 |

Correlation coefficients are shown. * $p < 0.05$; + $p < 0.01$; § $p < 0.001$
Abbreviations: Hemodialysis (HD), Myostatin (Mstn), Body mass index (BMI), Fat tissue index (FTI), lean tissue index (LTI), Overhydration (OH), C-reactive protein (CRP), McAuley index (McA), Malnutrition Inflammation Score (MIS)

failure patients with cachexia, such as in healthy old adults [9, 10, 23, 24]. Similarly, in HD patients, while Mstn has been found to be overexpressed in muscle and strictly linked to inflammation and muscle atrophy, the analysis of serum Mstn levels has shown contrasting results [13, 14, 22, 25]. Therefore, it seems there could be a discrepancy between muscular and circulating Mstn, whose explanation is not so clear. First, it is possible that circulating Mstn not necessarily reflects its intramuscular concentration, since the protein may be also produced from other tissues or undergoes degradation. Secondly, it is conceivable that other extracellular matrix proteins might interact with Mstn and Mstn-linked molecules, regulating Mstn expression and TGF-β signalling pathway in muscle cells [26].

However, when we looked at the functional meaning of serum Mstn, we did not find correlations among serum Mstn and functional tests exploring muscle strength, endurance and fatigue.

Analogously, when we studied the metabolic parameters, we did not find significant correlations among circulating Mstn and metabolic pathways, including lipids and insulin resistance (IR), evaluated by McAuley index. Also in this case, as well as for that reported for muscle mass, the relationship between circulating Mstn and IR is controversial and matter of debate. Indeed, while previous studies showed elevated Mstn levels in obese patients with hyperinsulinemia and IR, configuring a condition in which IR might potentiate the inhibitory effect of Mstn on muscle growth [27], high serum Mstn has also been reported to be associated with favourable metabolic profiles and a lower prevalence of metabolic syndrome [28].

Therefore, overall these findings indicate that while circulating Mstn seems to reflect the muscle mass, its actual clinical significance and utility in HD patients remains questionable.

Beyond data on Mstn, our study highlighted some other collateral findings that are worthy to be considered. First of all, we confirmed that malnutrition is very common in HD patients. In our study this condition, which actually implies a complex and multifaceted pathogenesis, resulted related to age, inflammation (evaluated as CRP levels) and overhydration (OH) state. In particular, the correlation of OH with malnutrition and inflammation has been also reported in other studies [29] and is of peculiar interest in HD patients, since volume control is one of the main problems in the daily management of these patients.

Regarding muscle function tests, we found that HGS was directly correlated with muscle mass, as also previously reported, and inversely related to age, while self-reported muscle fatigue correlated with malnutrition, which may probably represent the functional correspondent.

We are aware that our study presents some limitations, mainly due to the observational design and the small number of patients evaluated with control subjects younger than HD patients.

Indeed, while a single determination of circulating Mstn is related to muscle mass, it is possible that the periodical monitoring (i.e. the time trend) of Mstn levels could provide useful information about muscle loss and progression of cachexia over the time.

Moreover, it is conceivable that the study of complex processes, such as muscle wasting and malnutrition in HD, should not be limited to the evaluation of a specific marker.

For example, beyond Mstn, other molecules, such as cytokines, activins and follistatin, may regulate muscle growth and metabolism [30]. In particular, among them, Activin A, which shares the receptor with Mstn (i.e. ActRIIB) and has been related with muscle loss in cancer, seems worthy of being investigated as an additional biomarker of muscle wasting, also in HD patients [31, 32].

Finally, it should be underlined that the study of circulating Mstn could also be made difficult by technical limitations, since in the Literature there is some concern about the use of ELISA-based approaches to measure Mstn concentration, mainly because Mstn immunoreactivity does not necessarily equal to its bioactivity [33].

## Conclusions

In conclusion, we think that the relationship between Mstn and muscle mass and nutritional status candidate circulating Mstn as an interesting new player in the regulation of skeletal muscle trophism. This is particularly relevant, since Mstn is currently object of many researches on the potential role of its pharmacological inhibition, aiming to promote muscle mass increase and improve the metabolic profile and frailty in different disease conditions [34–36]. However, current evidence is not strong enough to support the use of serum Mstn to diagnose muscle wasting and malnutrition or to monitor the responses to the treatments in HD patients. Therefore, further studies, possibly prospective and performed with more accurate analytical methods (like mass spectrometry), are needed to elucidate the potentialities of circulating Mstn as a biomarker and its utility in detecting patients at risk for wasting.

### Abbreviations

6MWT: 6-min walking test; BHD: Bicarbonate hemodialysis; *BMI*: Body mass index; CKD: Chronic kidney disease; CRP: C-reactive protein; ELISA: Enzyme-linked immunosorbent assay; *ESRD*: End-stage renal disease; FSS: Fatigue Severity Scale; FTI: Fat tissue index; HD: Hemodialysis; HGS: Hand-grip strength; LTI: Lean Tissue Index; McA: McAuley index; MIS: Malnutrition Inflammation Score; Mstn: Myostatin; OH: Overhydration; spKT/V: standard pool KT/V

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### Authors' contributions

PE and ELP designed the study; EC, AA, MAG, GDN. carried out experiments; SP, NS, YB collected samples and analyzed the data; MG. made the figures; PE, RA, CL. and TR. drafted and revised the paper; all authors approved the final version of the manuscript.

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### Availability of data and materials

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

### Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Fondazione IRCCS Policlinico "San Matteo" of Pavia, Italy (n. 9358/2015). All participants have signed an informed consent.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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## Publisher's Note

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ORIGINAL ARTICLE

# Postural analysis in a pediatric cohort of patients with Ehlers-Danlos Syndrome: a pilot study

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## ABSTRACT

BACKGROUND: The Ehlers-Danlos Syndrome (EDS) is a rare disorder affecting the connective tissue. EDS patients may suffer of proprioception and balance impairment but all the studies dealing with such symptoms have been addressed to adult subjects. The Study of such impairment in younger patients may lead to a better awareness of own motor abilities and to a focused rehabilitative intervention. Therefore, our work aims to assess the occurrence of these alterations in a pediatric cohort of EDS patients.

METHODS: The Research was designed as a cross-sectional study with a matching control group and performed on a pediatric cohort of 12 subjects with Ehlers-Danlos Syndrome (Classic and Hypermobility type) and on 12 healthy controls, during a follow-up visit at the Department of Pediatrics and at the Rehabilitation Unit of the Foundation IRCCS Policlinico San Matteo, in Pavia from April 2015 to October 2015. A square forceplatform was used to obtain the CoP (center of pressure) displacement during quiet standing during an open and a closed eyes trials. The comparisons between EDS and control group were performed using a t-test for independent data. $P<0.05$ was considered statistically significant. All tests were two-sided.

RESULTS: All the postural parameters considered raised at closed eyes, no significant modifications without vision were found only for the standard deviation along the antero-posterior (AP) axis for the two groups. Both at open eyes and at closed eyes, Patients with EDS showed the postural parameters significantly greater than controls ($P\leq0.05$) and this observation was most notably for the Sway.

CONCLUSIONS: According to our results, a planned monitoring of age-related changes in postural parameters of patients with EDS could be really interesting to provide a perspective of the development of postural control in these patients. In fact, considering our results, it could be interesting to apply rehabilitative strategies to enhance motor coordination and postural reflexes so improving their postural control as soon as possible. Further studies about the postural control in EDS children and adolescents are required to confirm our results.

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KEY WORDS: Ehlers Danlos Syndrome; Pediatrics; Postural balance.

The Ehlers-Danlos Syndrome (EDS) gathers a group of monogenic inheritable disorders affecting the connective tissue. The main clinical features of the syndrome are: joints hypermobility, skin hyperextensibility, and tissue fragility.[1] The first description of a case evocative for EDS dates back even to Hippocrates, whereas the first medical report dealing with EDS was published in 1892 by the Russian physician Tschernogobow.[2] The syndrome was named after a Danish and a French dermatologist lived at the turn of the 19th century, Edvard Lauritz Ehlers and Henri-

Alexandre Danlos, who were the first to provide a comprehensive description of the phenotype.[3, 4] In 1949, studying familiar cases of EDS, Jonhson *et al.* concluded for EDS to be an autosomic dominant trait[5] and 7 years later, in 1956, McKusick included EDS among the hereditable disorders of connective tissue.[6] The first evidence of the molecular mechanisms involved in the syndrome was demonstred by Pinnell *et al*. in 1972,[7] when the deficit of lysil-hydroxylase was firstly described. The discovery of the underlying biochemical defects coupled with the complexity of the clinical phenotypes required a classification system. The first attempt to clarify the complex nosology of the EDS was the Villefranche classification (1998) as shown in Table I, which identified six different subtypes considering the manner of inheritance, the collagen defect and the clinical presentation.[1]

Depending the molecular basis of EDS and dissecting its phenotypical spectrum, new subtypes were identified, so that in 2012 De Paepe and Malfait presented a revised classification,[8] consisting of 12 subtypes (Table II).

The incidence of EDS is thought to be 1:5000 live birth, with a similar distribution between gender or ethnic groups.[9] Being EDS largely under-diagnosed, in particular for the milder subtype, epidemiological data are not reliable. EDS patients usually do not experience severe medical issues, except for abrupt vascular rupture in the vascular type. More subtle complications may occur in adulthood, such as recurrent pain and joint dislocation, osteoarthritis, dysautonomic disorders and psychological disfunctioning.[8] A new emerging chapter for EDS are neurological feature, as EDS subjects may suffer of headache, neuropathy, cerebrovascular accident or epilepsy.[9] Furthermore, as already highlighted by different authors,[10-13] EDS patients may suffer of proprioception and balance impairment, possibly conditioning abstention from physical activity, abnormal postures and traumatic injuries. To our knowledge, all the studies dealing with such symptoms in EDS have been addressed to adult subjects. Yet, the evidence of such impairment in younger patients may lead to a better awareness

TABLE I.—*The Villefranche EDS classification (1998) with six different subtypes of Ehlers-Danlos Syndrome, considering the manner of inheritance, the collagen defect and the clinical presentation.*

| Type | Inheritance | Mutated genes |
|---|---|---|
| Classic | AD | *COL5A1*,*COL5A2*, *COL1A1*, *TNXB* |
| Hypermobility | AD | unknown/*TNXB*? |
| Vascular | AD | *COL3A1* |
| Kyphoscoliosis | AR | *PLOD1* |
| Arthrochalasia | AD | *COL1A1*, *COL1A2* |
| Dermatosparaxis | AR | *ADAMTS2* |

AD: autosomal dominant; AR: autosomal recessive.

TABLE II.—*The De Paepe and Malfait EDS classification (2012) with 12 different subtypes of Ehlers-Danlos Syndrome, considering the molecular basis of EDS.*

| Type | Inheritance | Mutated genes |
|---|---|---|
| Classic | AD | *COL5A1*,*COL5A2*, *COL1A1*, *TNXB* |
| Hypermobility | AD | unknown/*TNXB*? |
| Vascular | AD | *COL3A1* |
| Kyphoscoliosis | AR | *PLOD1* |
| Arthrochalasia | AD | *COL1A1*, *COL1A2* |
| Dermatosparaxis | AR | *ADAMTS2* |
| Cardiac-valvular | AR | *COL1A2* |
| Vascular-like | AD | *COL1A1* |
| Musculocontractural | AR | *CHST14* |
| Spondylocheirodysplastic | AR | *SLC39A13* |
| Brittle cornea syndrome | AR | *ZNF469/PRDM5* |
| EDS/OI overlap | AD | *COL1A1/COL1A2* |

AD: autosomal dominant; AR: autosomal recessive.

of own motor abilities and to a focused rehabilitative intervention. Therefore, our work aims to assess the occurrence of these alterations in a pediatric cohort of EDS patients.

## Materials and methods

This cross-sectional study with a matching control group was performed on a pediatric cohort of 12 subjects with Ehlers-Danlos Syndrome, Classic and Hypermobility type and on 12 healthy controls, during a follow-up visit at the Department of Pediatrics and at the Rehabilitation Unit of the Foundation IRCCS Policlinico San Matteo, in Pavia from April 2015 to October 2015.

As summarized in Table III, the two study groups consisted of an EDS group of 6 males [(mean age 12.3 (sd: 5,5) years)]; [(Body Mass Index, BMI 17.10 (3.13) kg/m$^2$) ] and 6 females [(mean age 14.7 (5.08) years]; [BMI 16.5 (1.9) kg/m$^2$)] and a control group of 12 healthy subjects, 6 males [(mean age 13.7 (5.4) years)], [(BMI 17.7 (3.9) kg/m$^2$)] and 6 females [(mean age 15.5 (5.7) years)], [(BMI 18.7 (3.18) kg/m$^2$)].

Exclusion criteria were: previous spine a/o lower limbs surgery; learning disabilities; vestibular impairments; neurological disorders; visual defects not corrected with lenses.

The protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as revised in year 2000 and all participants' parents gave their informed consent to be involved in the study.

To obtain the displacement values of the CoP (center of pressure), a force platform Argo RGM® was used.

ARGO is a square platform with four load cells and with a sampling frequency of 100 Hz;[14] a dedicated software makes it possible to assess the CoP coordinates (*x, y*) when climbing on the platform itself.

All evaluations have been carried out by the same expert operator and all participants were instructed to climb on the force platform, without shoes, to maintain an upright position for 60 s, with arms at their sides and united feet, not to talk or move during each trial.

They started with a 60 s trial with open eyes (EO), than, after an interval of about 60 s, they proceeded with a second 60 s trial with closed eyes (EC). In order to avoid the adaptation phase in reaching the upright steady state, the first interval 5 s of each evaluation was discarded.[15]

The protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as revised in year 2000 and all participants' parents gave their informed consent to be involved in the study.

### Data analysis

As cited above, a computer-automated software allowed to transform ground reaction forces and moments along the two axis, antero-posterior and latero-lateral (AP and LL) into conventional parameters describing CoP displacement. The following measures were chosen: Sway path, expressed in mm/s; Sway area, mm$^2$/s; SD-standard deviation- of AP CoP excursion (AP sway, mm); SD of LL CoP excursion (LL sway, mm). We considered greater sway coefficients, greater postural instability.[10]

### Statistical analysis

Design study: cross-sectional study with a control sex and age (±2 years) matching group. Mean and standard deviation were calculated for quantitative variables, since they were normally distributed (Shapiro-Wilk Test). The comparisons between EDS and control group were performed using a *t*-test for independent data. $P<0.05$ was considered statistically significant. All tests were two-sided. The data analysis was performed with the STATA statistical package (release 14.0, 2015, Stata Corporation, College Station, TX, USA)

TABLE III.—*Clinical characteristics of EDS patients and control group.*

| | EDS patients (N.=12) | | Control group (N.=12) | |
|---|---|---|---|---|
| | M | F | M | F |
| N. (%) | 6 (50) | 6 (50) | 6 (50) | 6 (50) |
| Age (years; mean±SD) | 12.3±5.5 | 14.7±5.08 | 13.7±5.4 | 15.5±5.7 |
| BMI (kg/m$^2$; mean±SD) | 17.1±3.13 | 16.5±1.9 | 17.7±3.9 | 18.7±3.18 |

TABLE IV.—*Postural parameters of EDS group and control group. The four parameters are expressed as mean (standard deviation).*

| | EDS | Controls | P value |
|---|---|---|---|
| SD LL CoP (EO)mm | 5.43 (1.54) | 3.83 (0.97) | 0.005 |
| SD LL CoP (EC) | 7.12 (2.01) | 5.51 (1.83) | 0.05 |
| SD AP CoP (EO)mm | 5.87 (1.67) | 4.6 (1.03) | 0.03 |
| SD AP CoP (EC) | 5.83 (0.93) | 5 (1.5) | 0.13 |
| Sway path (EO)mm/s | 16.67 (5.53) | 11.7 (2.7) | 0.01 |
| Sway path (EC) | 25.22 (8.09) | 19.4 (5.6) | 0.05 |
| Sway area (EO)mm$^2$/s | 42.47 (24.91) | 19.83 (6.9) | 0.006 |
| Sway area (EC) | 72.67 (34.58) | 45.37 (23.38) | 0.03 |

SD: standard deviation; LL: latero-lateral; CoP: center of pressure; EO: open eyes; EC: closed eyes; AP: antero-posterior.

## Results

All values of the postural parameters considered in this study are reported in Table IV as mean and standard deviation.

Both for EDS and controls the four postural parameters considered raised at closed eyes, indicating a greater Cop displacement without the visual support (EC); no significant modifications without vision were found only for the standard deviation along the AP axis for the two groups.

At EO patients with EDS showed all the four postural parameters chosen significantly greater than controls ($P \leq 0.05$) and this observation was most notably for the Sway Area, which resulted double the average for EDS than controls (42.47±24.91 mm$^2$/s for EDS *vs.* 19.83±6.9 mm$^2$/s for controls), as in condition of less accurate postural control.

Even at closed eyes all the four postural parameters were significantly greater among EDS than Controls, except for the SD AP (5.83±0.93 for EDS *vs.* 5±1.5 for controls, P=0.13).

## Discussion

Our study focused on the evaluation of four postural parameters (Sway Path, Sway Area, SD AP and SD LL) of patients with EDS during the quiet standing and on the comparison of these parameters between the same group and a group of healthy volunteers.

To our knowledge, no studies about postural control in a pediatric cohort of patients with Ehlers-Danlos Syndrome were made before, although some authors concentrated on deficits in balance and gait in adults affected by EDS.[11-13]

In fact, it is well known that EDS is associated with an impaired postural stability[10, 13] and proprioceptive impairment.[16]

Galli *et al.*,[13] focusing on the postural control in Prader-Willi (PW) and EDS, showed an increase of CoP excursion both in ML and AP directions among these patients.

The same authors justified their results as an effect of muscle hypotonia and weakness in EDS and PW, which affected joint stability. Moreover, they hypothesized that ligament laxity, a major feature of many connective disorders including EDS, could be responsible of an increased range of motion of joints with a raised ankle instability in quiet standing also.

In 2011, Rombaut *et al.*[11] focused on balance and gait in EDS, by comparing a group of 22 EDS adults with a group of 22 controls matched for age, sex and ethnicity. They showed an increased CoP displacement among these patients as compared to controls, both during EO trials, both during EC trials with SDs of the means of the postural parameters considered about 2-7 times higher in EDS.

About the sensory impairment, Hall *et al.* were the first to demonstrate an altered proprioception among patients with Hypermobility Syndrome, by studying their threshold of degrees detection at knee flexion angles.

Rombaut *et al.*[10] found that patients with EDS presented an impaired joint position sense at the knee but not at the shoulder and that their tactile sensitivity was preserved when compared to healthy controls, so claiming that the major contribute to proprioceptive impairment in EDS could be given by tendon and joint receptors.

Recentely, Cleyton *et al.*[17] analyzed the ability

of a group of 9 EDS patients to localize their non dominant hand in the space and compared their results with those of thirteen healthy controls. They showed that EDS subjects were less precise about their hand's position than controls but the amplitude of error was not related to patients' chronic pain.

Our results confirm the presence of postural instability among an EDS pediatric cohort too.

In fact, our patients with EDS showed a higher displacement of the CoP than controls during EO and EC trials, particularly for the Sway Area, which was double the average for EDS patients, both at EO and EC, as in condition of less accurate postural control.

Instead controls, who presented an AP displacement higher or comparable to the ML displacement in all the trials, EDS patients showed an higher ML oscillation during the EC trial when compared to AP oscillation in the same visual condition, as reported in developmental disabilities.[18]

As cited by Rigoldi *et al.*,[19] "the increase in ML amplitude sway is considered as a predictor of postural instability." In that study, these authors investigated postural control among children, teenagers and adults with Down Syndrome, which is characterized by hypotonia and ligament laxity as well as EDS, and found only the onset of some postural abnormalities during the childhood. Differently, we reported the same motor impairment in children with EDS as compared to adult patients.

Lastly, the SDs of the Sway Path at EO and EC were much more higher for EDS than controls, suggesting an high variability in postural control impairment in the EDS sample.

### Limitations of the study

While claiming that this is a pilot study, we point out that our work has some limitations: the small sample, although EDS is a rare disease, and the wide age range. We specify that the statistical analysis of results was made by comparing all patients with controls matched for sex, age, height and BMI.

## Conclusions

To our results, a planned and careful monitoring of age-related changes in postural parameters of patients with EDS could be really interesting to provide a perspective of the development of postural control in these patients.

Moreover, by considering that an impaired postural stability has been found in children with EDS also, it could be interesting to apply rehabilitative strategies to enhance motor coordination and postural reflexes so improving their postural control as soon as possible.

Further studies about the postural control in EDS children and adolescents are required to confirm our results.

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ORIGINAL ARTICLE

# Functional assessment and rehabilitation protocol in acute patients affected by SARS-CoV-2 infection hospitalized in the Intensive Care Unit and in the Medical Care Unit

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## ABSTRACT

BACKGROUND: Coronavirus disease (COVID-19) is characterized by different clinical pictures that may require prolonged hospitalization and produce disabilities challenging the recovery of previous independence.
AIM: The aim is to evaluate the impact of an early assisted rehabilitation program on the functional status of an acutely hospitalized population affected by COVID-19.
DESIGN: Single-institution retrospective longitudinal study.
SETTING: Inpatient intensive care units (ICU) and medical care units (MCU).
POPULATION: Acute COVID-19 patients.
METHODS: General information was collected; age-adjusted Charlson Comorbidity Index was used for comorbidities. Duration of hospital stay, the length of stay in ICU and/or MCU, the length of the rehabilitative treatment, and the destination at the discharge were collected. Evaluation was performed when patients were clinically stable (T0), and at hospital discharge (T1); for subjects enrolled in ICU functional status was assessed at the time of transfer to the MCU. Muscle strength of the four limbs was measured with the Medical Research Council (MRC) sum-score. Functional status was assessed using the 3-item Barthel Index (BI-3) and the General Physical Mobility Score (GPMS). Early assisted-tailored rehabilitation protocol was applied in ICU and in MCU: the aims were the maintenance (or recovery) of the range of motion and of the strength and the recovery of sitting/standing position and gait.
RESULTS: We evaluated 116 patients (mean age 65, SD 11) (65% male), 68 in ICU (mean age 60, SD 10), 48 in MCU (mean age 73, SD 9). At discharge, BI-3 and GPMS significantly improved in both ICU ($P<0.001$) and MCU ($P<0.001$) subgroups of patients. MRC sum-score significantly improved in ICU patients ($P<0.001$). Patients hospitalized in ICU had a significantly longer hospital stay. At discharge, patients admitted to the ICU reach a functional state that is close to that of patients admitted to the MCU.
CONCLUSIONS: The results suggest that an early assisted rehabilitation program may be helpful in improving the short-term functional status of an acutely hospitalized population affected by COVID-19, with discharge at home of 48%
CLINICAL REHABILITATION IMPACT: this study focuses on a functional assessment method to be used to identify the rehabilitation needs and verify the results of an early rehabilitation protocol applied to the acute COVID-19 patient admitted to ICU and MCU.

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KEY WORDS: COVID-19; SARS-CoV-2; Rehabilitation.

Coronavirus disease (COVID-19) is an infectious disease first detected in Wuhan, China. It first appeared in Italy in January 2020, the first case with secondary transmission being diagnosed in February 2020. In March 2020, W.H.O. declared a pandemic state.[1] COVID-19 is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and is characterized by a broad spectrum of clinical features, ranging from a complete absence

of symptoms to mild symptoms such as fever, cough, fatigue, headache, myalgia, gastrointestinal disorders and anosmia up to dyspnea in case of bilateral pneumonia of varying grade of severity.[2-5] COVID-19, whose symptoms are marked by the expression of the viral infection and by the host's anti-inflammatory response, can progress into three pathophysiological stages: the infection phase, the pulmonary phase and the inflammatory phase.[3-8] In severe cases, interstitial pneumonia may be accompanied by multiorgan failure and by phenomena of thrombosis, microangiopathic skin lesions at the extremities and disseminated intravascular coagulation.[7] The compromise of respiratory function may express itself with pictures of different severity requiring oxygen therapy or non-invasive ventilatory assistance; in case of acute respiratory distress syndrome (ARDS), invasive mechanical ventilation with prolonged hospitalization in intensive wards is required.[2, 3] In addition to advanced age and male gender, comorbidities such as type 2 diabetes, hypertension, obesity and pre-existing impaired immune function are considered risk factors for the development of a severe SARS-CoV-2 infection.[6]

Patients with severe pictures of SARS-CoV-2 infection may therefore require prolonged hospitalization in intensive care unit (ICU) which, as already reported in the literature regarding patients with respiratory disease not related to COVID-19, is cause of myopathy with loss of body mass of about 20% after the first week and with rhabdomyolysis, hypotrophy and hyposthenia being due to mitochondrial dysfunction and metabolic alterations in the satellite cells that are necessary for muscle regeneration.[9-12] Moreover, muscle atrophy is in turn a complication of hypercapnia due to lung damage.[13] The pathophysiological mechanisms of ICU-acquired weakness are believed to be multifactorial and muscle damage is associated with neuronal damage and axonal degeneration from microcirculatory dysfunction.[11] In ICU-acquired weakness neuromuscular recovery is delayed and 65% of patients have been estimated to have functional limitation at the discharge, the neuromuscular damage lasting for years.[14, 15] Previous reports about severe form of Coronavirus 1 infection have shown long recovery times, even 12 years, in case of critical illness.[6]

In order to reduce the effects of prolonged immobility and to improve functional outcomes, rehabilitation is actually considered an integral part of the management of critically ill patients.[16-18]

With the spread of the covid 19 pandemic, greater knowledge on the clinical characteristics, treatment and sequelae of this pathology have led to a growing scientific literature regarding the rehabilitation approach of the SARS-CoV-2 patient, and a series of systematic rapid living reviews on rehabilitation needs has been published. The main fields of intervention concern the rehabilitation treatment of acute respiratory failure that characterizes the initial stages of the disease, the containment of the effects related to prolonged immobility with an early mobilization of the patient admitted to the ICU, the recovery of mobility prior to hospitalization through continuation of rehabilitation treatment both in the postacute phase and at home, where continuous monitoring of the motor, neurological, cognitive sequelae is necessary.[19, 20]

The aim of this study is to evaluate the impact of an early assisted rehabilitation program on the functional status of an acutely hospitalized population affected by COVID-19.

## Materials and methods

### Population and study design

This study was conducted as a single-institution retrospective longitudinal study and was performed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Guidelines. It was approved by the local ethical board ("Area Vasta Pavia" Bioethics Committee, protocol number: 20200069920 - date of approval: 05/08/2020) and was drawn up in accordance with the current version of the World Medical Association Declaration of Helsinki (2013). For informed consent to study participation we refer to the consent that all patients sign upon admission to the ICU or MCU ward, as approved by the bioethics committee. The trial was carried out in accordance with the standards of good clinical practice.

Data were collected, from March to June 2020, on subjects admitted to COVID Units of the IRCCS Policlinico San Matteo Foundation (Pavia, Lombardia, Italy) with a diagnosis of COVID-19 related pneumonia. COVID Units included Intensive Care Units (ICU) and Medical Care Units (MCU). As soon as the patients were considered clinically stable, they were evaluated for inclusion in an assisted rehabilitation program (see procedures for details) by a Physical and Rehabilitation Medicine (PRM) specialized physician both in ICU and in MCU. Inclusion criteria were: age 18 or older and a diagnosis of COVID-19 related pneumonia. ICU patients were included with a diagnosis of COVID-19 related pneumonia with ARDS (in phase of weaning from mechanical ventilation). Exclusion criteria

were a previous diagnosis of neuromuscular diseases and general contraindications to mobilization (cardiorespiratory or neurological instability, need for Extra Corporeal Membrane Oxygenation assistance).

### Procedures

As part of the recruitment procedure, general information was collected on basic demographics and the burden of previous clinical history was determined using the age-adjusted Charlson Comorbidity Index.[21, 22] The PRM clinical evaluation included sensorium, general compliance, active and passive motility of all four limbs, sitting/standing position and gait (if possible). We specifically measured muscle strength in all four limbs, applying the Medical Research Council (MRC) sum-score, one of the most commonly used clinical grading tool to assess global muscle strength.[23, 24] The MRC sum-score is the summation of the strength of six muscle groups (arm abduction, elbow flexion, wrist extension, hip flexion, knee extension and ankle dorsiflexion), bilaterally tested according to the MRC scale.[25] The sum-score ranges from 0 to 60 points, the range 0-36 indicating severe muscular weakness, the range 36-48 indicating significant muscular weakness.[23, 24] The functional evaluation (see outcome section for details) was performed at the first PRM evaluation (T0) and at the discharge from hospital (T1); for subjects enrolled in ICU and then transferred to MCU, the functional status and the MRC sum-score were also assessed at the discharge from ICU. We also registered the total duration of hospital stay, the length of stay in ICU and/or MCU, the length of the rehabilitative treatment (expressed as number of sessions of physiotherapy) and the destination at the discharge.

The early rehabilitation project had two aims: the maintenance (or recovery) of the range of motion and of the strength and the recovery of sitting/standing position and gait. The exercise program involved daily a 30-minute session assisted by a physiotherapist. In Table I, II we reported the stages of the rehabilitation program we carried out in ICU and MCU respectively.

### Outcome assessment

As primary outcome, the functional status was assessed using the 3-item Barthel index (BI-3) and the General Physical Mobility Score (GPMS). The Barthel Index is a worldwide known standard measure of functional ability.[26] Information on functional status is essential for assessing rehabilitation practice, but during COVID-19 spreading, it was impractical to obtain a full assessment in the acute units, so we chose the BI-3, a simplified and validated alternative to the full Barthel score, based on three items

TABLE I.—*Rehabilitation protocol in Intensive Care Covid Units.*

| |
|---|
| Intensive Care Units rehabilitation program |
| 1- Postural alignment in bed of the head, neck, trunk, shoulder and pelvic girdle; |
| 2- Passive/active assisted range of motion exercises of the upper and lower limbs. Selective exercises on the shoulder girdle musculature without involving the pelvic girdle, and *vice versa*; |
| 3- If the patient is intubated *via* tracheostomy, passive mobilization of the cervical spine; awareness of the oral cavity by mobilizing the tongue and the temporomandibular joint; |
| 4- Active exercises to strengthen the muscles of the upper and lower limbs |
| 5- Balance bed exercises of the trunk, shoulder and pelvic girdle in the sitting position in bed; gradual recovery of the sitting position at the edge of the bed; training in the upright standing position and gradual recovery of the bed-chair transition |
| 6- Reached the standing position, walking training with load transfer and walking on the spot with direct assistance or supervision |
| 7- Cognitive exercise for the tidal volume breathing pattern; sequential breathing exercise Active Cycle of Breathing Techniques |
| Transfer to Medical Care Units |
| 1- Continuation of the motor rehabilitation program performed in ICU until ambulation is recovered |
| 2- Sequential breathing exercise Active Cycle of Breathing Techniques, breathing exercises in a sitting position, incentive spirometers using volume - oriented device. |

TABLE II.—*Rehabilitation protocol in Medical Care Covid Units.*

| |
|---|
| 1- Passive/active assisted range of motion exercises of the upper and lower limbs; exercise for cervical spine |
| 2- Active exercises to strengthen the muscles of the upper and lower limbs |
| 3- Balance bed exercises of the trunk, shoulder and pelvic girdle in the sitting position in bed; gradual recovery of the sitting position at the edge of the bed, training in the upright standing position and gradual recovery of the bed-chair transition |
| 4- Reached the standing position, walking training with load transfer and walking on the spot with direct assistance or supervision until ambulation is recovered |
| 5- Sequential breathing exercise Active Cycle of Breathing Techniques, breathing exercises in a sitting position, incentive spirometers using volume - oriented device. |

TABLE III.—*General Physical Mobility Score (GPMS).*

| |
|---|
| 0= patient confined to bed |
| 1= patient performs movements on the bed |
| 2= patient reaches the sitting position on the edge of the bed |
| 3= patient reaches the upright position |
| 4= patient walks with assistance |
| 5= patient walk independently |

only (transfers, walking, bladder control). The BI-3 is reported to predict total Barthel Index score in around 90% of cases.[27] The GPMS was instead created as a new tool, made up of single item, in order to assess in more detail than the item "transfers" of the BI-3 the maximum grade of ability in autonomously performing transfers (Table III).

As secondary outcomes, we assessed variations of MRC sum-score in the ICU subgroup of patients at the first PRM evaluation (T0) and at the transfer to MCU. Moreover, we assessed differences in terms of length of hospital stay and functional status at discharge between patients admitted in ICU and those admitted in MCU. Finally, we evaluated the impact of functional status on the destination at discharge.

### Statistical analysis

The Shapiro-Wilk Test was used to test the normal distribution of quantitative variables. If normally distributed, the results were expressed as mean and standard deviation (SD), otherwise median and interquartile range (IQR: 25-75$^{th}$ percentiles); qualitative variables were summarized as counts and percentages.

Functional outcomes (BI-3 and GPMS) are compared between admission and discharge (separately in ICU and MCU patients) with paired *t*-test.

Multivariate linear regression models were fitted to evaluate the effect of the length of the rehabilitative treatment on improvement of functional outcome (BI-3 and GPMS); covariate were sex and age-adjusted Charlson Index and being admitted to ICU. Results are expressed as coefficient with their 95% confidence interval (CI) and presented with term specific P values; the coefficient represents the mean variation of outcomes for unit change of quantitative predictors or between levels of categorical or ordinal predictors.

For MRC sum score multi level linear regression with patients as random factors are fitted to evaluate the effect of the length of the rehabilitative treatment on improvement of this functional outcome covariate were sex and age-adjusted Charlson Index. Results are expressed as coefficient with their 95% CI and presented with term specific P-values; the coefficient represents the mean variation of outcomes for unit change of quantitative predictors or between levels of categorical or ordinal predictors.

For MRC sum score categories multi level ordinal logistic regression with patients as random factors are fitted to evaluate the effect of the length of the rehabilitative treatment on improvement of this functional outcome covariate were sex and age-adjusted Charlson Index. Results are expressed as as odds ratio (OR) with their 95% CI and presented with term specific P values.

Multivariate logistic regression models are fitted to evaluate effect of improvement of functional outcome on discharge at home (covariate sex age-adjusted Charlson Index). Results are expressed as OR with their 95% CI and presented with term specific P values.

P values <0.05 were considered to be statistically significant. Data analysis was performed with STATA statistical package (release 16.1, 2013, Stata Corporation, College Station, TX, USA).

## Results

### Descriptive data

General characteristics of the population at the first PRM evaluation are described in Table IV.

The rehabilitative program was generally well tolerated by the patients. In subjects diagnosed for thrombosis or pulmonary embolism after the beginning of the rehabilitation protocol, assisted physiotherapy was stopped and started again 48 hours after the beginning of a proper anticoagulant therapy. Two subjects presented hematomas, respectively located at the thigh and at the iliopsoas, but they regularly followed the protocol.

In five ICU patients, a critical illness polyneuropathy and miopathy was clinically diagnosed and confirmed by an EMG/ENG examination during the hospital stay. A per-

TABLE IV.—*Demographic, anamnestic ad functional characteristics of the population.*

| Sample (N.) | ICU subgroup (68) | MCU subgroup (48) | All patients (116) |
|---|---|---|---|
| Age, years (SD) | 60 (10) | 73 (9) | 65 (11) |
| Sex, male (%) | 51 (75) | 25 (52) | 76 (65) |
| Charlson Comorbidity Index (SD) | 1 (0-2) | 1.5 (1-2) | 1 (0-2) |
| BI-3 median (range) | 0 (0-2) | 0 (0-7) | 0 (0-7) |
| GPMS median (range) | 0 (0-2) | 1 (0-4) | 0 (0-4) |
| MRC sum-score (SD) | 23 (12) | 41 (8) | 31 (13) |

Value are expressed as means±SD and as median (IQR) for continous data and counts (percentage) for categorica data. ICU: Intensive Care Unit; MCU: Medical Care Unit; BI-3: 3-item Barthel Index; GPMS: General Physical Mobility Score; MRC sum-score: Medical Research Council sum score.

sistent clinical picture of ICU acquired weakness at discharge from hospital was observed in further thirteen ICU cases. Finally, two subjects presented neurological complications, respectively a Guillain-Barré Syndrome and a facial nerve paralysis.

### Primary outcome

The BI-3 total score and the GPMS showed a statistically significant improvement in both ICU (P<0.001) and MCU (P<0.001) subgroups of patients, as reported in Figure 1, 2 respectively.

Regarding the regression analysis, the length of the rehabilitative treatment (BI-3 beta 0.07 for 1 day increase 95%CI 0.01-0.12 P=0.014; GPMS beta 0.03 95%CI 0.01-0.06 P≥0.015) and the age-adjusted Charlson Index (P<0.001) are significantly positively and negatively correlated to the improvement of functional outcome.

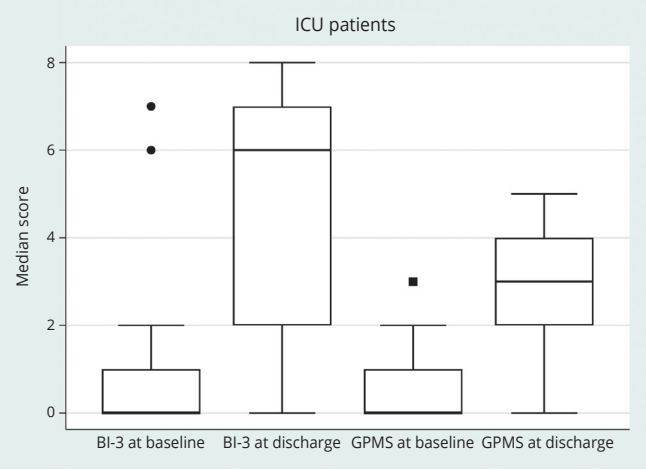


Figure 1.—BI-3 total score and GPMS score at baseline and at discarge in ICU patients.

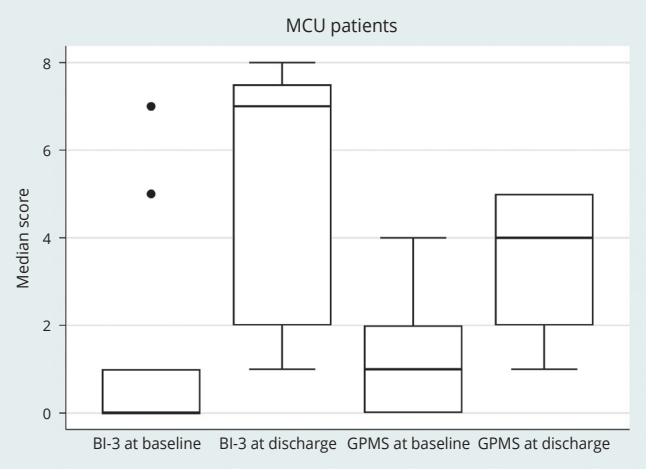


Figure 2.—BI-3 total score and GPMS score at baseline and at discarge in MCU patients.

### Secondary outcome

Data about monitoring of MRC sum-score in ICU patients are summarized in Figure 3.

MRC sum-score significantly improved in ICU (P<0.001). For what regards the regression analysis, the length of the rehabilitative treatment (beta 0.29 for 1 day increase; 95%CI 0.06-0.53 P=0.012) is also significantly correlated to the improvement of muscular strength. On the contrary, the MRC sum-score variation resulted negatively affected by the burden of comorbidity, the coefficient value decreasing by -3,7 points as the age-adjusted Charlson Index point-by-point increase. Analysing the MRC sum-score by categories (0-36, 36-48, 48-60), results about the influence of the cited variables did not change (Figure 4).

Total duration of the hospital stay, the length of stay in ICU and/or MCU, the length of the rehabilitative treatment and the destination at the discharge are listed in Table V.

Patients hospitalized in ICU had a significantly longer hospital stay. At discharge, patients admitted to the ICU reach a functional state that is close to that of patients admitted to the MCU. The improvement of functional outcome (BI-3) (OR 1.67 95%CI 1.33-2.10 P<0.001), the age-adjusted Charlson Index (P<0.001) and ICU stay (P<0.001) are significantly positively and negatively correlated to discharge to home.

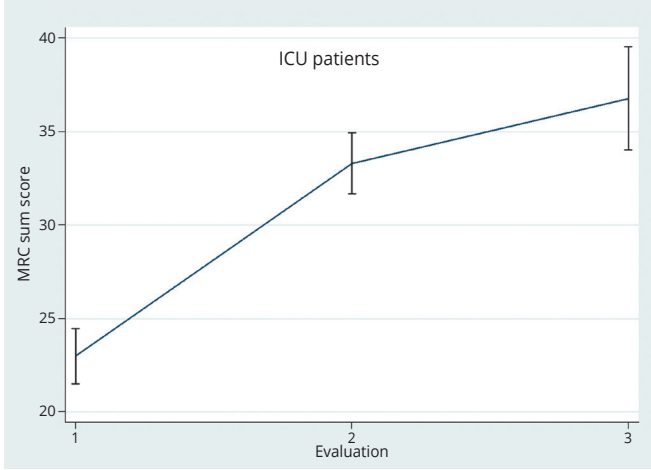


Figure 3.—Monitoring of MRC sum score in ICU patients.

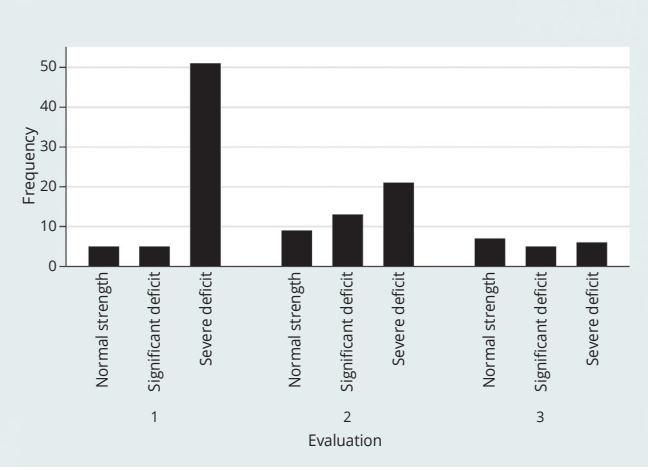


Figure 4.—Monitoring of MRC sum score categories in ICU patients.

TABLE V.—*Duration of the hospital stay, length of the rehabilitative treatment, destination at the discharge.*

| Sample (N.) | ICU subgroup (68) | MCU subgroup (48) | All patients (116) |
|---|---|---|---|
| ICU hospital stay, days median (IQR) (available only for ICU subgroup) | 36 (28-50) | - | - |
| Total Hospital stay, days median (IQR) | 50 (38-67) | 29 (21-37) | 41 (26-57) |
| Rehabilitative treatment session median (IQR) | 12 (9-20) | 6 (4-9) | 10 (5-16) |
| Discharged to Subacute Units (%) | 42 (62) | 12 (27) | 54 (48) |
| Discharged to home (%) | 21 (31) | 33 (73) | 54 (48) |
| Dead (%) | 5 (7) | 0 | 5 (4) |

Value are expressed as median (IQR) for continous data and counts (percentage) for categorica data. ICU: Intensive Care Unit; MCU: Medical Care Unit.

## Discussion

The results of this observational study highlight a major impairment of functional status in patients with severe SARS-CoV-2 infection that required hospitalization, however with a significant functional improvement at discharge the degree of the improvement being correlated to comorbidity and to the length of the rehabilitative treatment.

Our early, structured and assisted rehabilitation protocol was feasible, tailored to the patient and continued throughout the hospital stay.

As reported by Curci *et al.*, postacute COVID-19 patients admitted to the Rehabilitation Unit from ICU presented a severe disability in terms of pulmonary function and motor impairment for which an early rehabilitation treatment adapted to the clinical conditions becomes necessary. The need of rehabilitation care already in the acute stages of COVID-19 disease is reported in the scientific literature that has grown with the spread of the COVID-19 pandemic.[28] McWilliams *et al.* report that rehabilitation protocols implemented in intensive care on patients with stabilized clinical picture lead to increased levels of mobility before ICU discharge.[29]

Despite the severity of the COVID-19 and the geriatric average age (65 years) of the sample, 48% of the patients were discharged home. Despite patients hospitalized in ICU resulted to have a significantly longer hospital stay and a major exposure to prolonged immobility, we observed in this subgroup of patients a significant and progressive improvement of MRC sum-score, with a changeover from a severe muscular weakness (0-36) to a significant muscular weakness (36-48) during the rehabilitative treatment.

During the COVID-19 pandemic outbreak in March 2020, the urge to provide a rehabilitative support to an increasing number of patients and lack of scientific evidence about the rehabilitative treatment of subject affected by COVID-19 infection, led us to plan, in a short space of time, a rehabilitative program based on our skills and previous clinical experience in treating acutely hospitalized patients.[16, 17, 30-34]

Subjects hospitalized in ICU because of a SARS-CoV-2 infection usually show a respiratory impairment similar to patients affected by ARDS of different etiologies, the typical restrictive pulmonary picture requiring respiratory support and, in some cases, bringing to delayed weaning from mechanical ventilation and to prolonged hospitalization in intensive wards. As direct consequence, we observed a progressive and diffuse muscular hypotrophy, with concomitant weakness to the trunk and the four limbs, sometimes leading to the most severe picture of the critical illness polyneuromyopathy. Moreover, prolonged mechanical ventilation cause diaphragm muscle atrophy with concomitant hyposthenia and further lengthening of the weaning procedures.[35] The infection related inflammatory state, the multiorgan involvement and the use of sedatives and neuromuscular blocking drugs worsen, in turn, muscular weakness into a complex motor impairment, requiring a rehabilitative intervention, aimed to recover muscle strength, sitting/standing position and gait. Considering that the loss of muscle strength is greatest in the first week of immobility,[36] the rehabilitative intervention should begin as early as possible. Moreover patients with COVID-19 demonstrated improved mobility at hospital discharge and higher probability of discharging home with

increased frequency and longer mean duration of physical therapy treatment.[37]

Patients hospitalized in MCU also showed a partial loss of muscle strength, caused by the concomitant action of inflammatory state, hypoxemia and stay in isolation wards. Besides, evidences from literature clearly reported a reduction of general mobility during hospital stay for any reason.[38] On that basis, the beginning of the rehabilitative treatment should be early and adaptable to the rapid evolution of clinical conditions in MCU too. Moreover, we suggest to educate patients to repeat active exercises during day time and to preserve their functional skills ("transfers" and activities of daily living), depending on the need to stay in isolation wards. The learning process of a rehabilitative program during the hospital stay allows patients discharged home to carry on their exercises in order to complete their functional recovery.

Analyzing MRC sum-score data, patients hospitalized in ICU showed a severe muscular weakness (0-36); those hospitalized in MCU showed instead a significant muscular weakness (36-48). Despite patients hospitalized in ICU resulted to have a significantly longer hospital stay and a major exposure to immobility, we observed in this subgroup of patients a significant and progressive improvement of muscular strength during the rehabilitative treatment, as a proof that an early participation in a rehabilitative program is helpful in limiting the sequelae of prolonged immobility and in facilitating functional recovery, as showed by the improvement of BI-3 and GPMS total score. The GPMS resulted to be an easy-to-fill in tool, useful in assessing patients' skills to perform "transfers" and residual functional needs.

The discharge from hospital to home is considered an optimal indicator of functional recovery: in the present study, despite the geriatric age of the sample, 48% of the patients were discharged to home. In the subgroup hospitalized in MCU, the percentage of patients discharged to home resulted to be 73%, in spite of a major number of comorbidities and average age (73 years).

### Limitations of the study

The present study has several limitations. For ethical reasons we could not plan a placebo-controlled trial with a control group (not performing rehabilitation), since we enrolled subjects with COVID-19 related functional limitation during an emergency time. Consequently, we couldn't demonstrate the full efficacy of the intervention on the observed functional evolution, in particular on muscle recovery and on discharge at home.

The lack of a longer follow-up prevented further consideration about long-lasting functional limitations in patients affected by COVID-19 related pneumonia. We also have to specify that we chose the 3-item Barthel Index and the GPMS to assess function for practical reasons only (in an emergency setting). Further studies, with a controlled design and with a more exhaustive functional evaluation are certainly justified to better understand the efficacy of rehabilitation in this context.

## Conclusions

In patients affected by COVID-19 related pneumonia the respiratory impairment is often associated to a progressive muscular weakness with a concomitant loss of function. An early rehabilitation treatment, tailored to the clinical setting and adaptable to the rapid evolution of clinical conditions is desirable to be applied in acute patients with SARS-CoV-2 infection.

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