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Fibromyalgia: Pathogenesis, Mechanisms, Diagnosis and Treatment Options Update

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Fibromyalgia: A Review of the Pathophysiological Mechanisms and Multidisciplinary Treatment Strategies

[Lina Noelia Jurado-Priego](#)¹, [Cristina Cueto-Ureña](#)¹, [María Jesús Ramírez-Expósito](#)¹, [José Manuel Martínez-Martos](#)^{1,*}

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[Michael Gyorfi](#)^{1,*}, [Adam Rupp](#)², [Alaa Abd-Elsayed](#)¹

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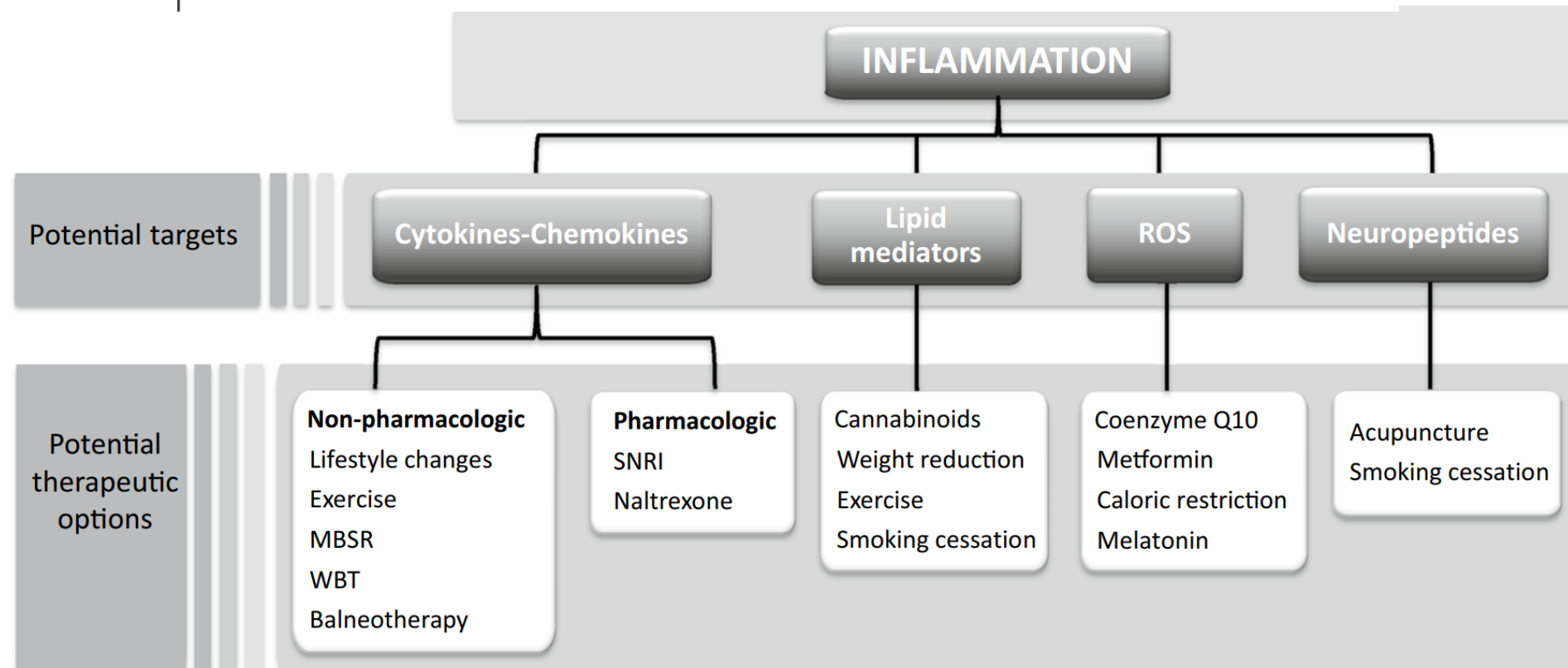
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Role of inflammation in the pathogenesis and treatment of fibromyalgia

Ilke Coskun Benlidayi¹

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A systematic review of the association between fibromyalgia and functional gastrointestinal disorders

[Sharon Erdrich](#) ^{1,✉}, [Jason A Hawrelak](#) ², [Stephen P Myers](#) ³, [Joanna E Harnett](#) ⁴

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High Prevalence of Restless Legs Syndrome among Patients with Fibromyalgia: A Controlled Cross-Sectional Study

[Mari Viola-Saltzman](#)¹, [Nathaniel F Watson](#)^{2,3,✉}, [Andy Bogart](#)⁶, [Jack Goldberg](#)⁴, [Dedra Buchwald](#)⁵

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➤ [Pain](#). 2017 Oct;158(10):1971-1978. doi: 10.1097/j.pain.0000000000000994.

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Jia-Chi Wang ¹, Fung-Chang Sung, Mauranda Men, Kevin A Wang, Cheng-Li Lin, Chia-Hung Kao

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Prevalence of restless legs syndrome in patients with irritable bowel syndrome

[P Patrick Basu](#)^{1,2,3,4}, [N James Shah](#)^{1,2,3,4}, [Nithya Krishnaswamy](#)^{1,2,3,4}, [Tommy Pacana](#)^{1,2,3,4}

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Review Article

Bidirectional association between irritable bowel syndrome and restless legs syndrome: a systematic review and meta-analysis

Jing Guo^{a,1}, Lixia Pei^{a,1}, Lu Chen^a, Hao Chen^b, Dongmei Gu^a, Yongjun Peng^a  ,
Jianhua Sun^a  

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➤ [J Urol](#). 2010 Oct;184(4):1358-63. doi: 10.1016/j.juro.2010.06.005. Epub 2010 Aug 17.

Interstitial cystitis/painful bladder syndrome and associated medical conditions with an emphasis on irritable bowel syndrome, fibromyalgia and chronic fatigue syndrome

[J Curtis Nickel](#) ¹, [Dean A Tripp](#), [Michel Pontari](#), [Robert Moldwin](#), [Robert Mayer](#), [Lesley K Carr](#), [Ragi Doggweiler](#), [Claire C Yang](#), [Nagendra Mishra](#), [Jorgen Nordling](#)

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PMID: 20719340 DOI: [10.1016/j.juro.2010.06.005](#)

The relationship between fibromyalgia and interstitial cystitis.

Clauw DJ ¹ , Schmidt M , Radulovic D , Singer A , Katz P , Bresette J

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“Zooming” in the association between rosacea and fibromyalgia syndrome: is it worth mentioning?

[Sevgi Kulaklı](#)¹, [Işıl Deniz Oğuz](#)¹, [Ilker Fatih Sarı](#)², [Ilker Sengul](#)^{3,4,*}, [Fazıl Kulaklı](#)², [Burak Akşan](#)¹, [Demet Sengul](#)⁵

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Review

> [Nutrients](#). 2022 Dec 24;15(1):90. doi: 10.3390/nu15010090.

Show Me What You Have Inside–The Complex Interplay between SIBO and Multiple Medical Conditions–A Systematic Review

Natalia Sroka ¹, Alicja Rydzewska-Rosołowska ¹, Katarzyna Kakareko ¹, Mariusz Rosołowski ², Irena Głowińska ¹, Tomasz Hryszko ¹

Association among Disorders of Gut-Brain Interaction (DGBI) and Fibromyalgia: A Prospective Study

[Carmela Settembre](#)¹, [Elvira D'Antonio](#)¹, [Paolo Moscato](#)², [Gabriella Loi](#)², [Antonella Santonicola](#)^{1,*†}, [Paola Iovino](#)

^{1,*†}

Figure 2. Prevalence of subtypes of FD among FM patients. FM: fibromyalgia; FD: functional dyspepsia; PDS: postprandial distress syndrome; EPS: epigastric pain syndrome.

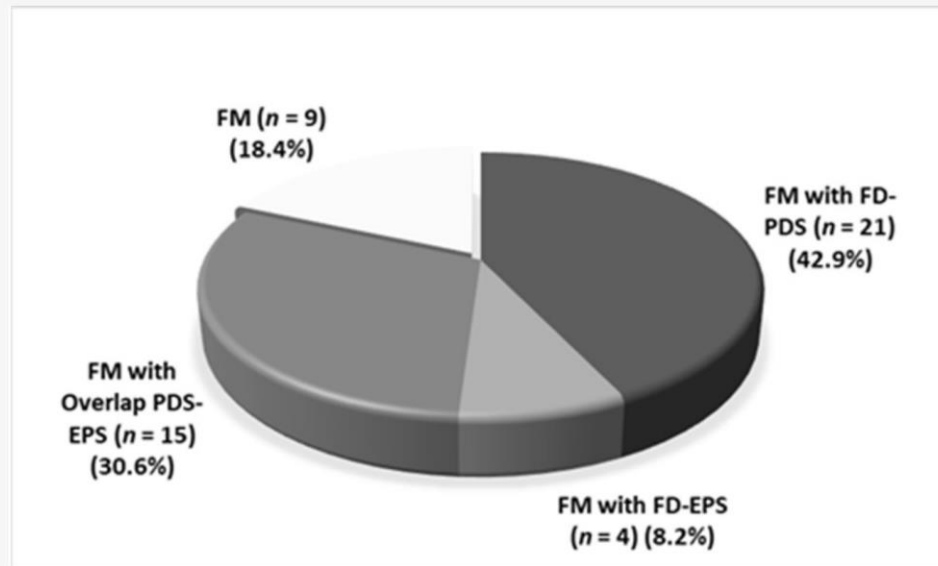
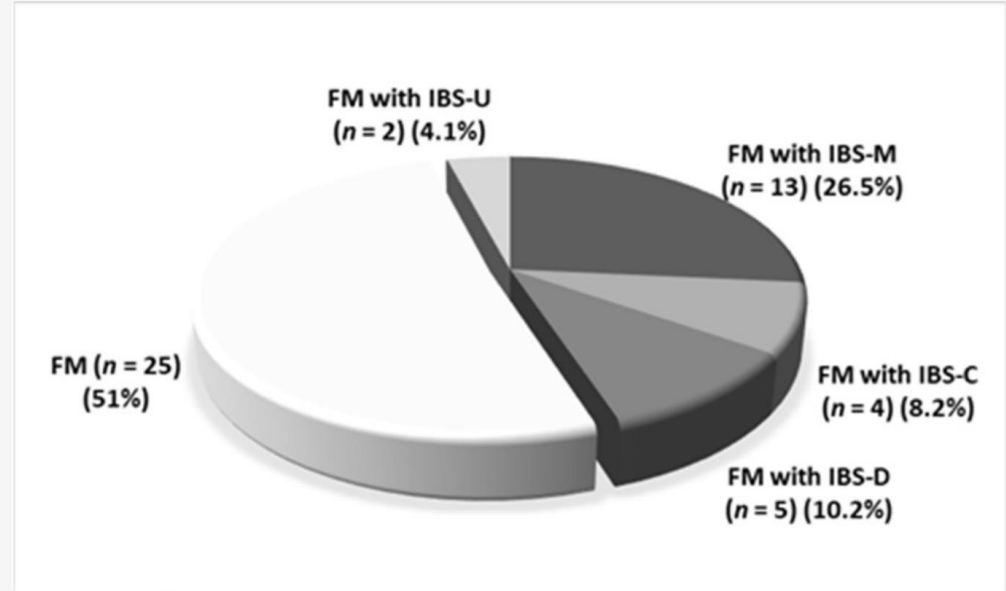


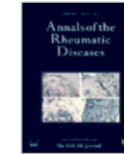
Figure 1. Prevalence of subtypes of IBS among FM patients. FM: fibromyalgia; IBS: irritable bowel syndrome; IBS-U: undetermined IBS; IBS-M: mixed IBS; IBS-C: constipation predominant IBS; IBS-D: diarrhea predominant IBS.





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Volume 63, Issue 4, April 2004, Pages 450-452



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D. VEALE, G. KAVANAGH, J. F. FIELDING, O. FITZGERALD ✉

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Worldwide Fibromyalgia Prevalence

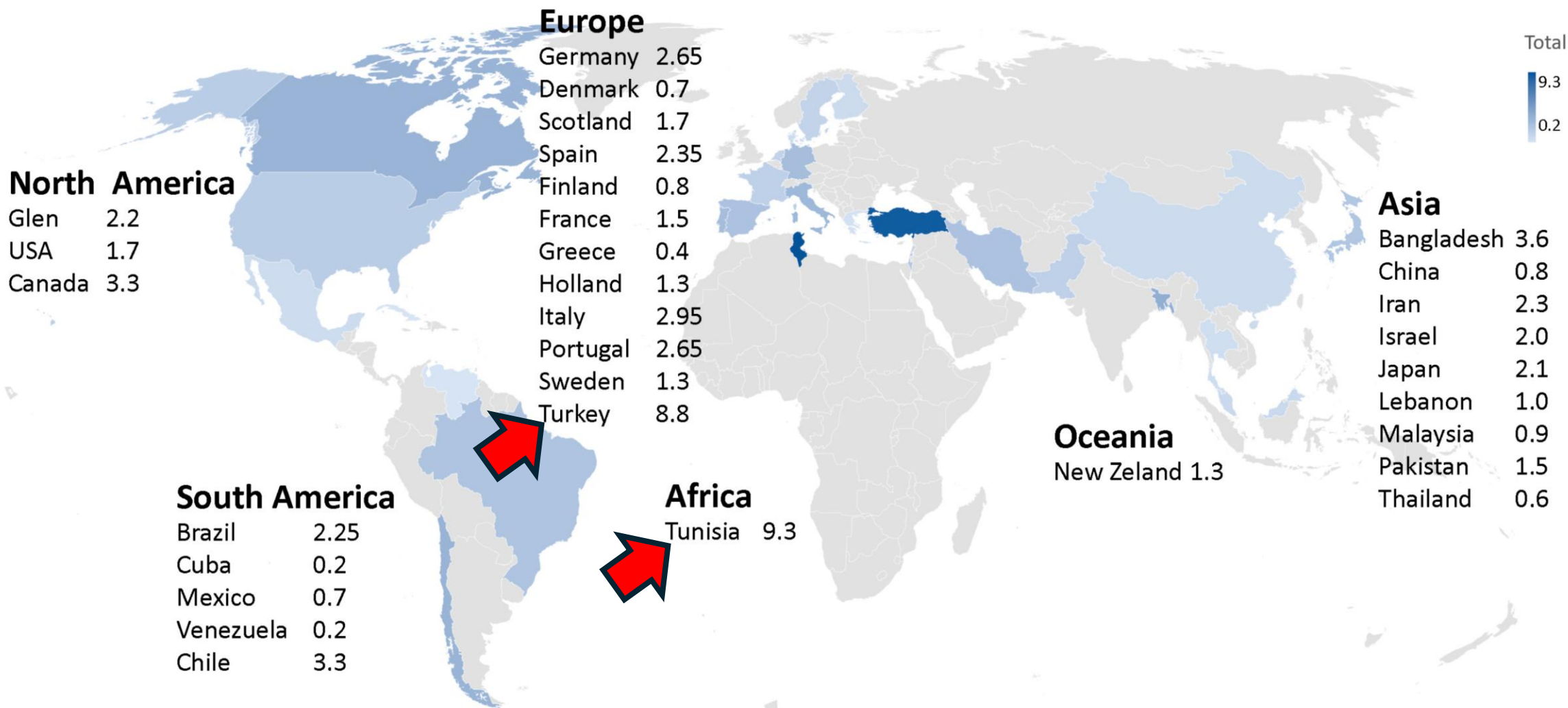
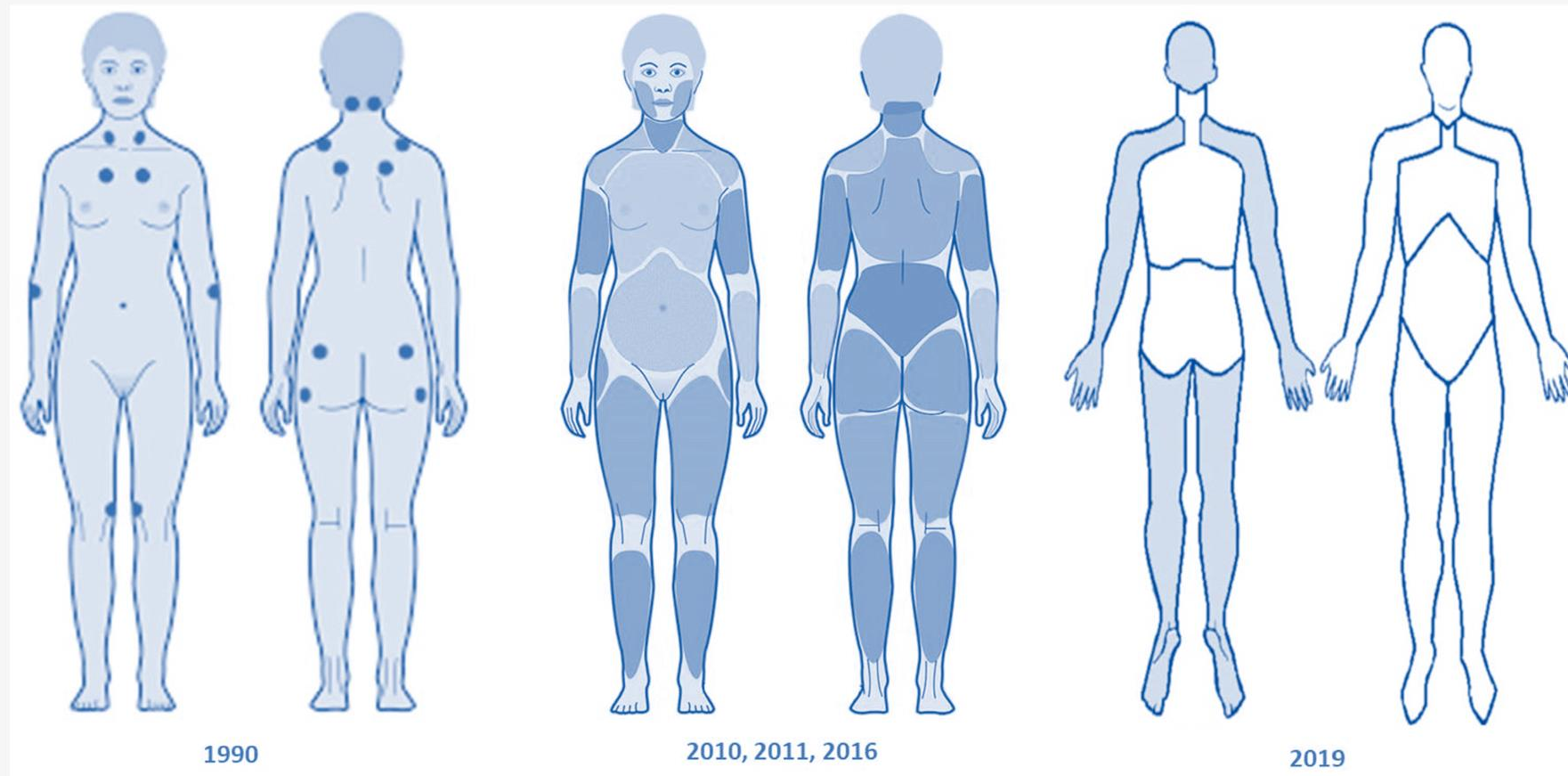


Figure 3. Evolution of classification criteria for diagnosing fibromyalgia across different years. The diagnosis and assessment of fibromyalgia have evolved over time. The American College of Rheumatology initially proposed criteria focusing on generalized pain and pain sensitivity. The 2010–2011 criteria interpreted fibromyalgia as a syndrome of multiple symptoms, emphasizing widespread pain and symptom severity. In 2016, a review incorporated four criteria: widespread pain, generalized pain, symptoms duration, and pain and symptom severity scores.



► [Biomedicines](#). 2022 Nov 29;10(12):3070. doi: [10.3390/biomedicines10123070](https://doi.org/10.3390/biomedicines10123070) [↗](#)

Fibromyalgia Pathophysiology

[Michael Gyorfi](#)^{1,*}, [Adam Rupp](#)², [Alaa Abd-Elsayed](#)¹

Editor: Hideya Kawasaki

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PMCID: PMC9776089 PMID: [36551826](#)

Abstract



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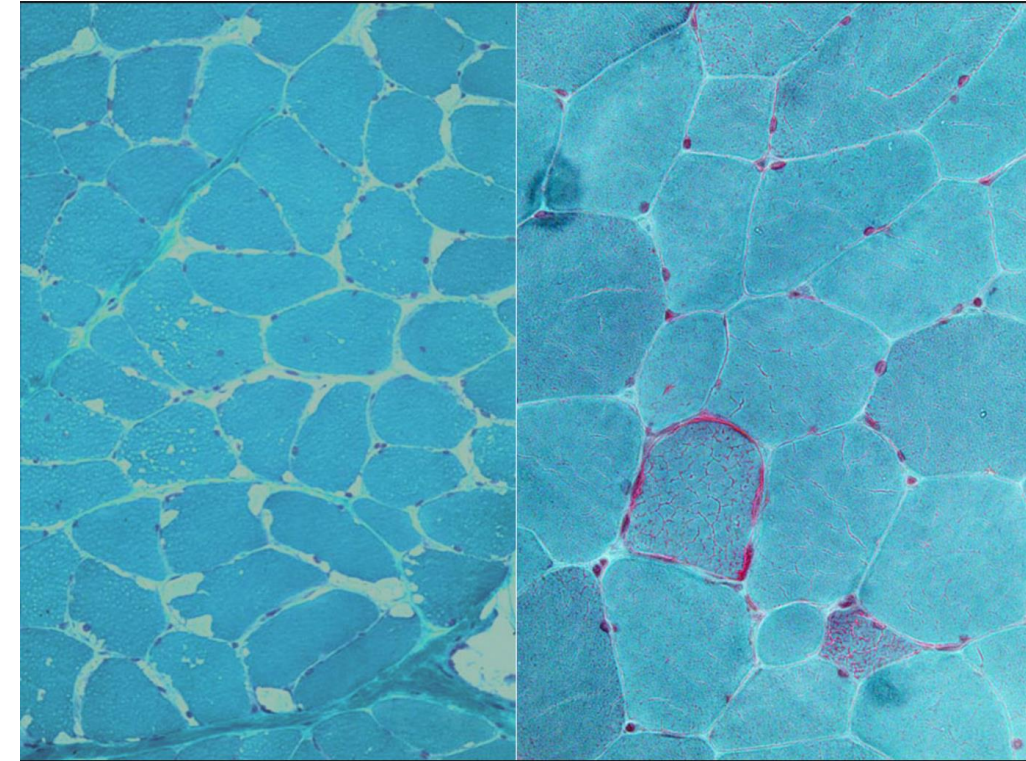
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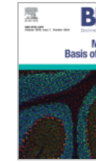
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Mitochondrial dysfunction and mitophagy activation in blood mononuclear cells of fibromyalgia patients: implications in the pathogenesis of the disease

Mario D Cordero ¹, Manuel De Miguel, Ana M Moreno Fernández, Inés M Carmona López,

- **FM hastalarının kaslarında** bir dizi **histopatolojik** bozukluk
- **Mitokondriyal myopatiler** için tipik bulgular
- «Ragged red fibriller»,
- Glikojen ve lipid birikimi
- Mitokondri sayısında düşme
- Kapiller endotelde kalınlaşma





Role of mitochondrial dysfunction and biogenesis in fibromyalgia syndrome: Molecular mechanism in central nervous system

Ylenia Marino ^a✉, Francesca Inferrera ^a✉, Ramona D'Amico ^a✉, Daniela Impellizzeri ^a✉,
Marika Cordaro ^b✉, Rosalba Siracusa ^a✉, Enrico Gugliandolo ^c✉, Roberta Fusco ^a  ✉

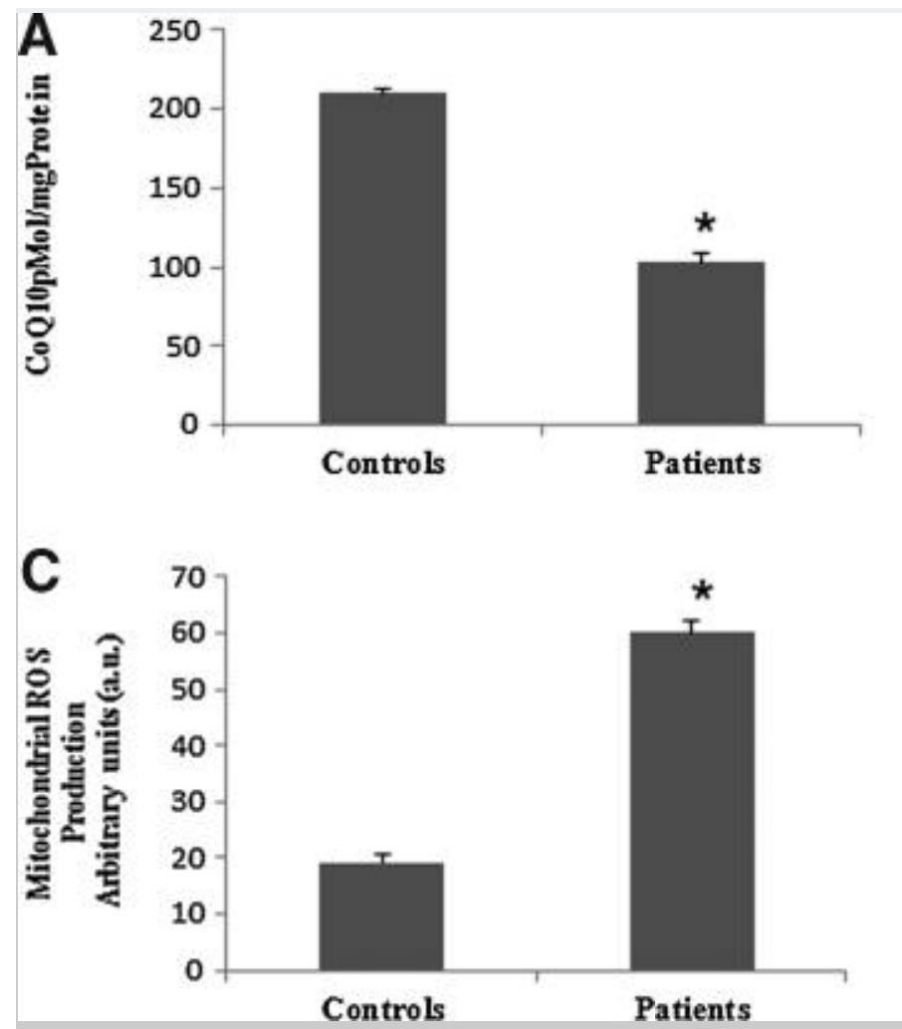
› [Antioxid Redox Signal](#). 2013 Mar 1;18(7):800-7. doi: 10.1089/ars.2012.4892. Epub 2012 Nov 16.

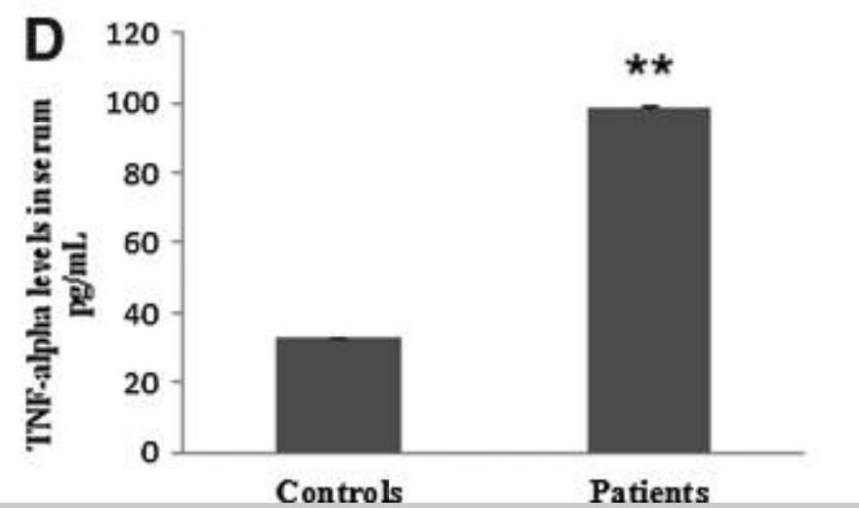
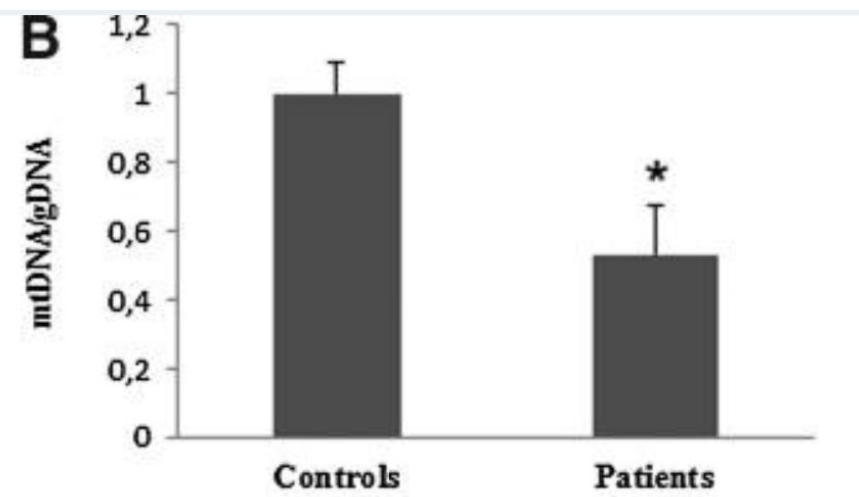
Is inflammation a mitochondrial dysfunction-dependent event in fibromyalgia?

Mario D Cordero ¹, Eduardo Díaz-Parrado, Angel M Carrión, Simona Alfonsi, José Antonio Sánchez-Alcazar, Pedro Bullón, Maurizio Battino, Manuel de Miguel

Affiliations + expand

PMID: 22938055 PMCID: [PMC3555092](#) DOI: [10.1089/ars.2012.4892](#)





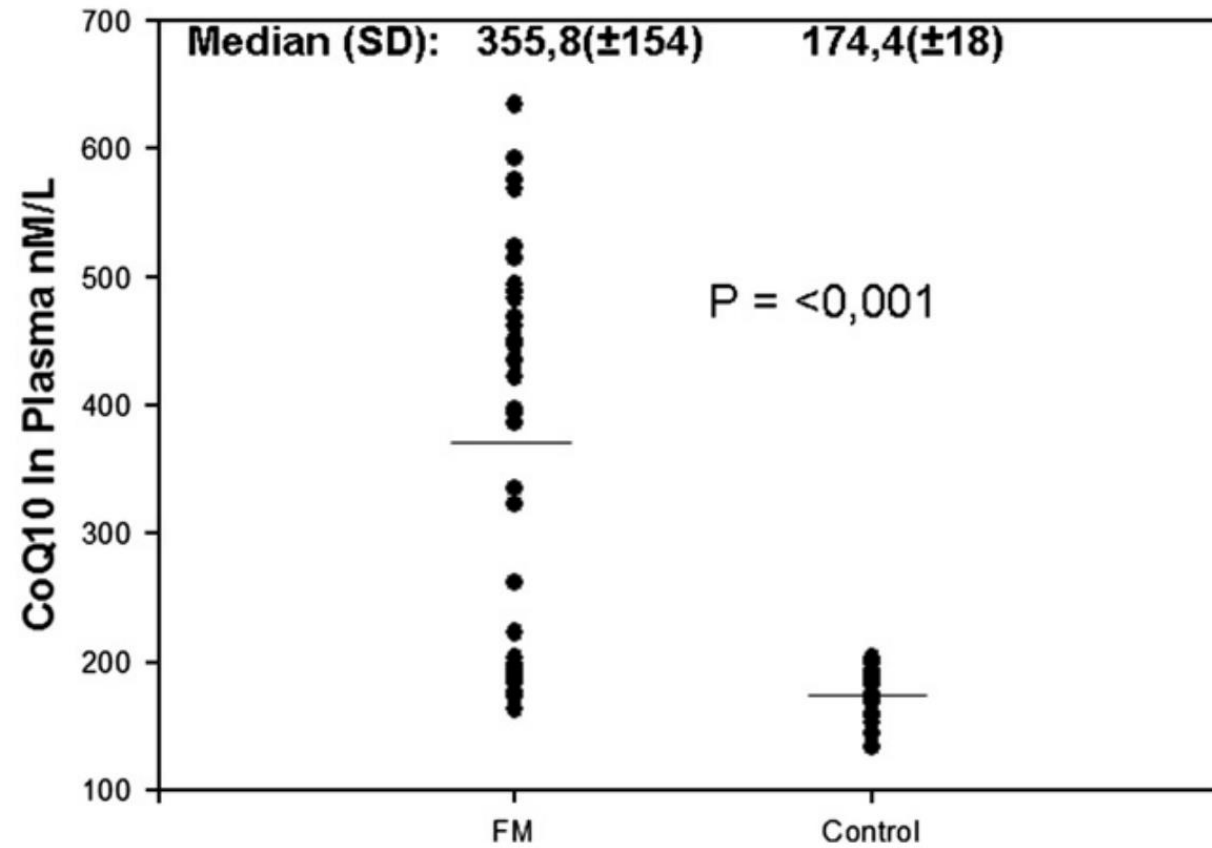
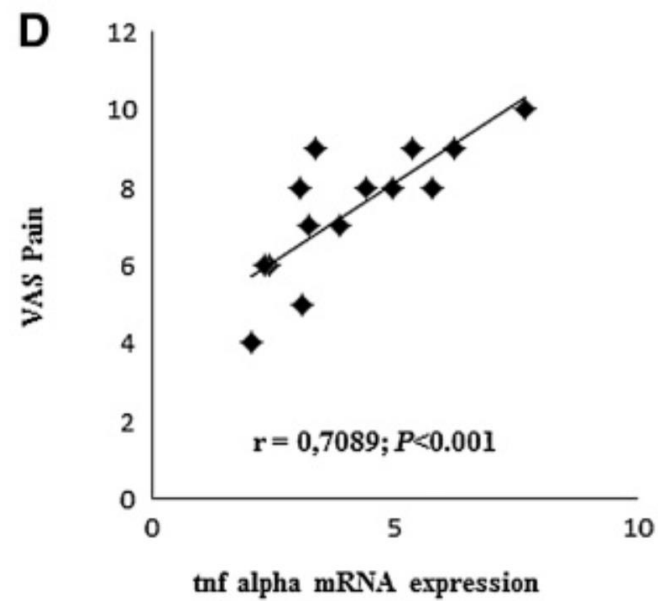
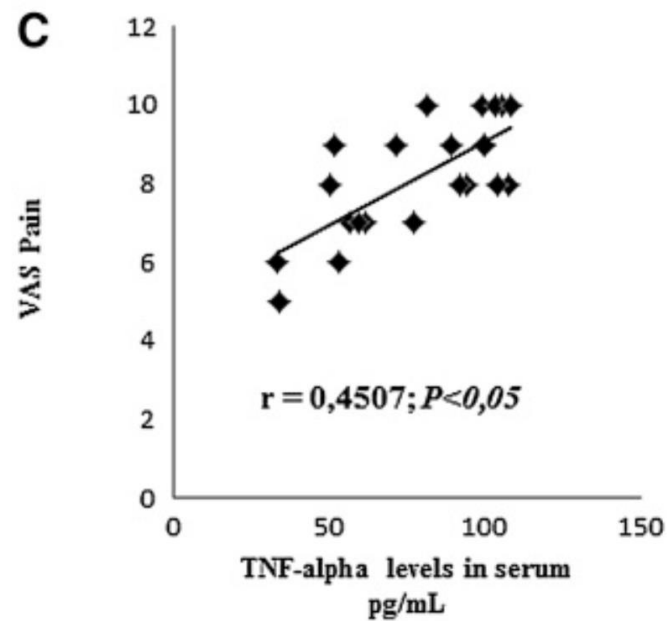
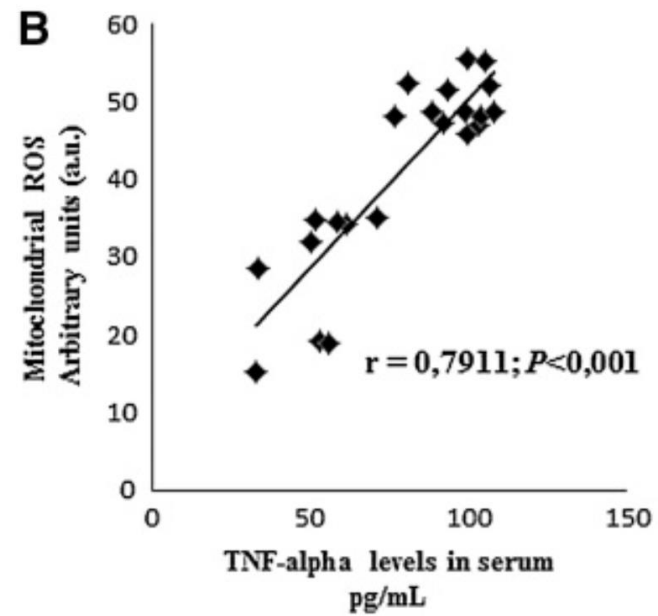
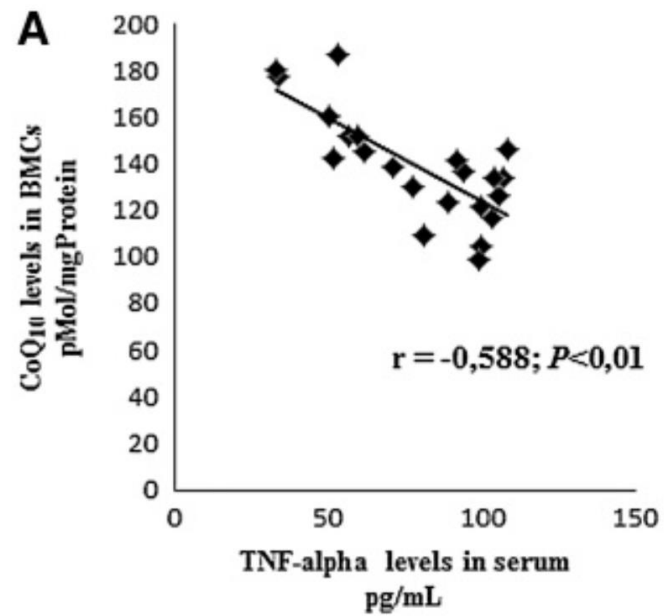


Fig. 1. Coenzyme Q10 levels in plasma from fibromyalgia patients and healthy control subjects. The analysis of CoQ₁₀ content in FM patients shows a significant increase of the concentration relative to control samples.



Epub 2011 Apr 7.

Coenzyme Q(10): a novel therapeutic approach for Fibromyalgia? case series with 5 patients

Mario D Cordero ¹, Elisabet Alcocer-Gómez, Manuel de Miguel, Francisco Javier Cano-García, Carlos M Luque, Patricia Fernández-Riejo, Ana María Moreno Fernández, José Antonio Sánchez-Alcazar

Table 1
Laboratory and clinical changes in

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
	Pre/post	Pre/post	Pre/post	Pre/post	Pre/post
Tender points	16/7	12/5	15/6	16/9	14/7
VAS total score, range 0–10	7/3	6/2	5/2	7/3	6/3
FIQ total score, range 0–80	61/26	51/20	65/30	53/38	56/23
HIT-6 total score, range 0–78	66/41	63/45	66/36	No	No
MIDAS total score, range 0–21+	73/31	65/27	70/29	No	No
LP in plasma (nmol/mL)	18.4/4.1	17.1/3.8	17.7/2.3	16.2/3.3	17.9/4.6
LP in BMCs (nmol/million cells)	25.1/13.4	26.7/11.4	28.8/10.2	27.3/12.1	27.6/11.4
CoQ ₁₀ (pMol/mg Protein)	109.1/234.1	114.1/241.9	135.9/263.4	117.9/222.2	123.3/231.7

Pre/post: pretreatment and posttreatment with CoQ₁₀; VAS: Visual Analogical Scale of pain; FIQ: Fibromyalgia Impact Questionnaire; HIT 6: Headache Impact Test; MIDAS: Migraine Disability Assessment; LP: lipid peroxidation; CoQ₁₀: Coenzyme Q₁₀.

Table 2. Clinical symptoms and biochemical markers after CoQ₁₀ treatment.

	Pre-treatment (n=10)	Post-treatment (n=10)	Control levels (n=15)
Tender points	13.9±1.2	9±0.5 ₋ [*]	---
FIQ total score, range 0–100	59.2±4.2 ₋ [†]	30.1±2 ₋ [*]	7.1±1.4
VAS, range 0–10	7.1±1.2 ₋ [†]	3.5±0.8 ₋ [*]	0.8±0.3
HIT-6, range 36–78	60.8±1.4 ₋ [†]	36.9±1.7 ₋ [*]	36.1±1.1
CoQ ₁₀ (pmolQ/mg protein)	135.6±6.3 ₋ [†]	221.6±11.3 ₋ [*]	224.4±12.3
ATP (nmol/mg protein)	61.3±4.9 ₋ [†]	191.1±6.7 ₋ [*]	202.8±22.1
Catalase (U/mg protein)	35.6±10.1 ₋ [†]	85.2±15.3 ₋ [*]	96.5±14.8
MDA in BMCs (nmol/million cells)	30.3±5.9 ₋ [†]	5.1±1.6 ₋ [*]	6±1

Randomized Controlled Trial > Free Radic Res. 2019 Aug;53(8):901-909.

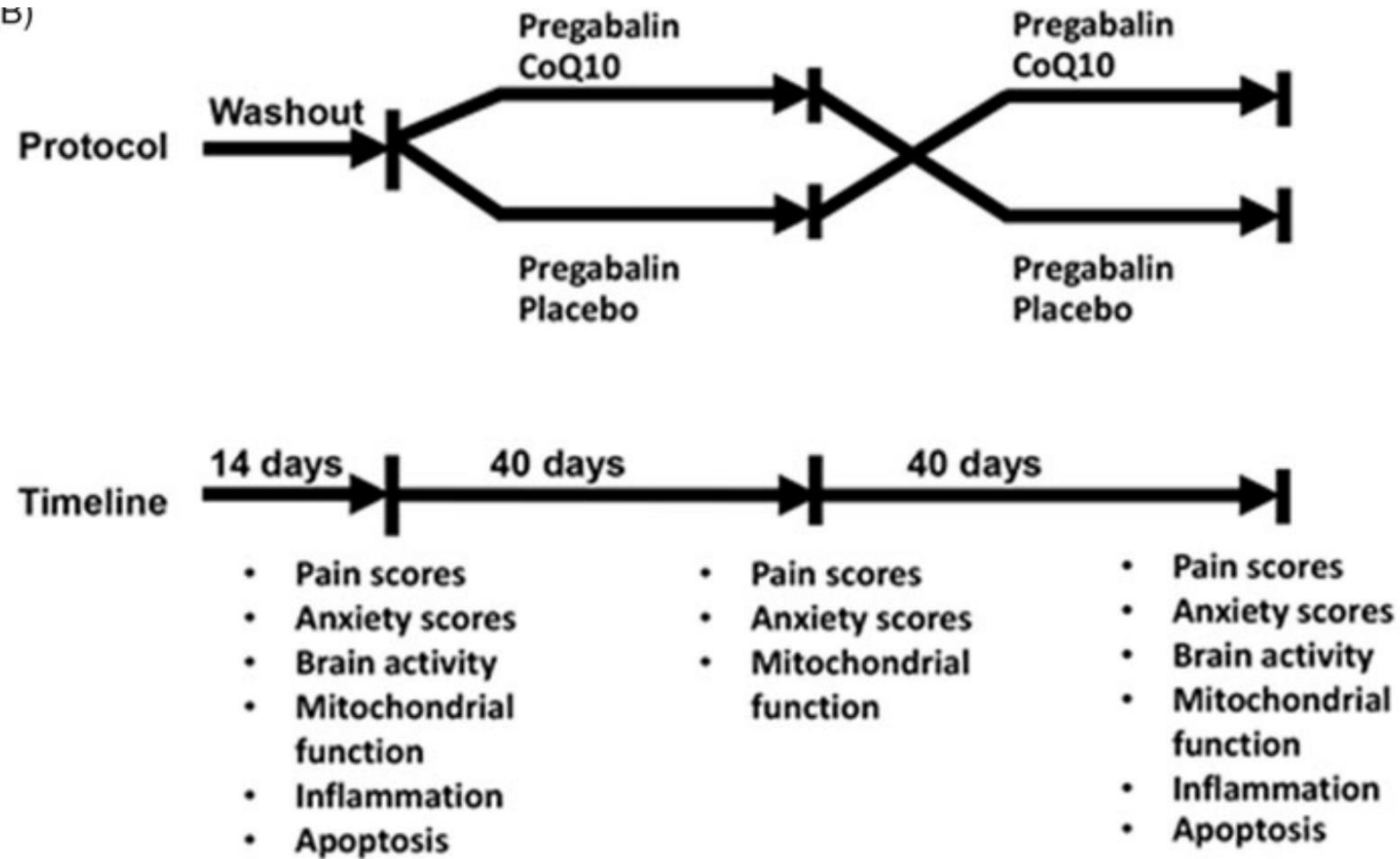
doi: 10.1080/10715762.2019.1645955. Epub 2019 Aug 7.

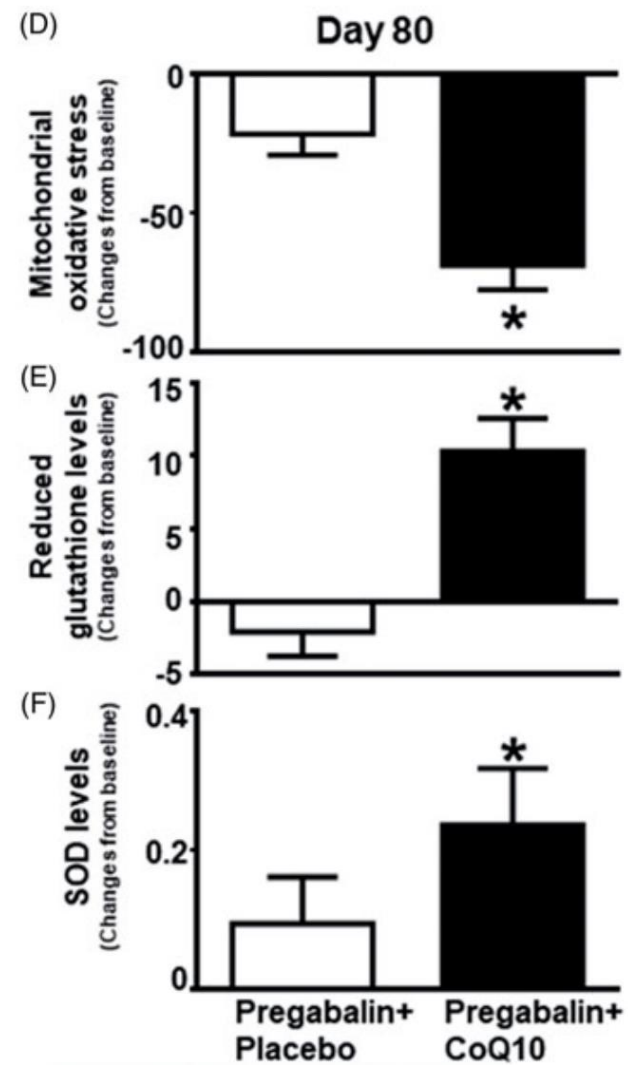
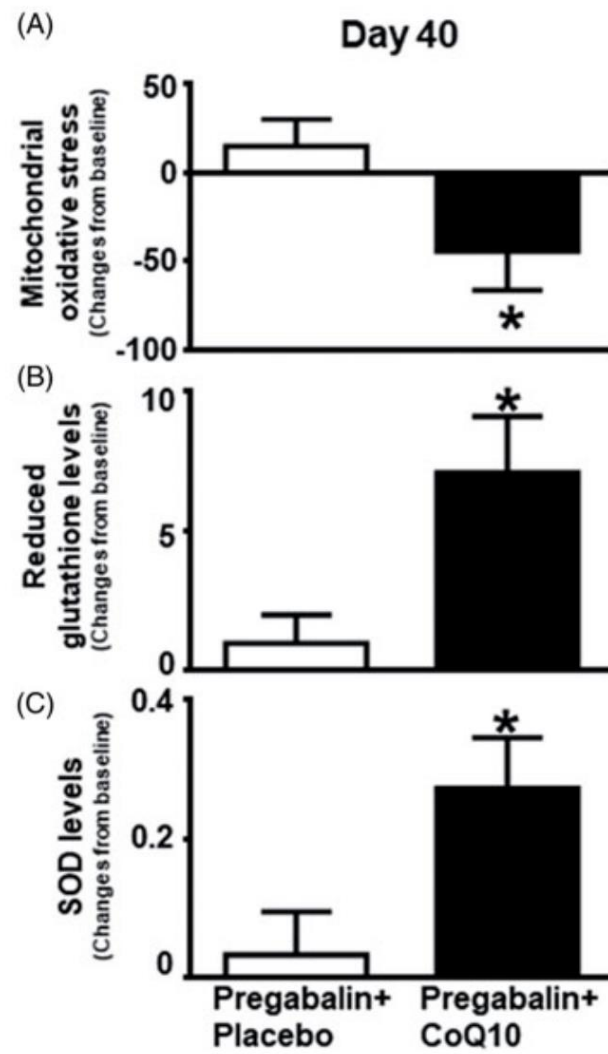
Coenzyme Q10 supplementation alleviates pain in pregabalin-treated fibromyalgia patients *via* reducing brain activity and mitochondrial dysfunction

Passakorn Sawaddiruk^{1 2 3}, Nattayaporn Apaijai^{1 2}, Sahattaya Paiboonworachat³,
Tawika Kaewchur⁴, Nuntana Kasitanon⁵, Thidarat Jaiwongkam^{1 2}, Sasiwan Kerdphoo^{1 2},
Nipon Chattipakorn^{1 2 6}, Siriporn C Chattipakorn^{1 2 7}

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(B)





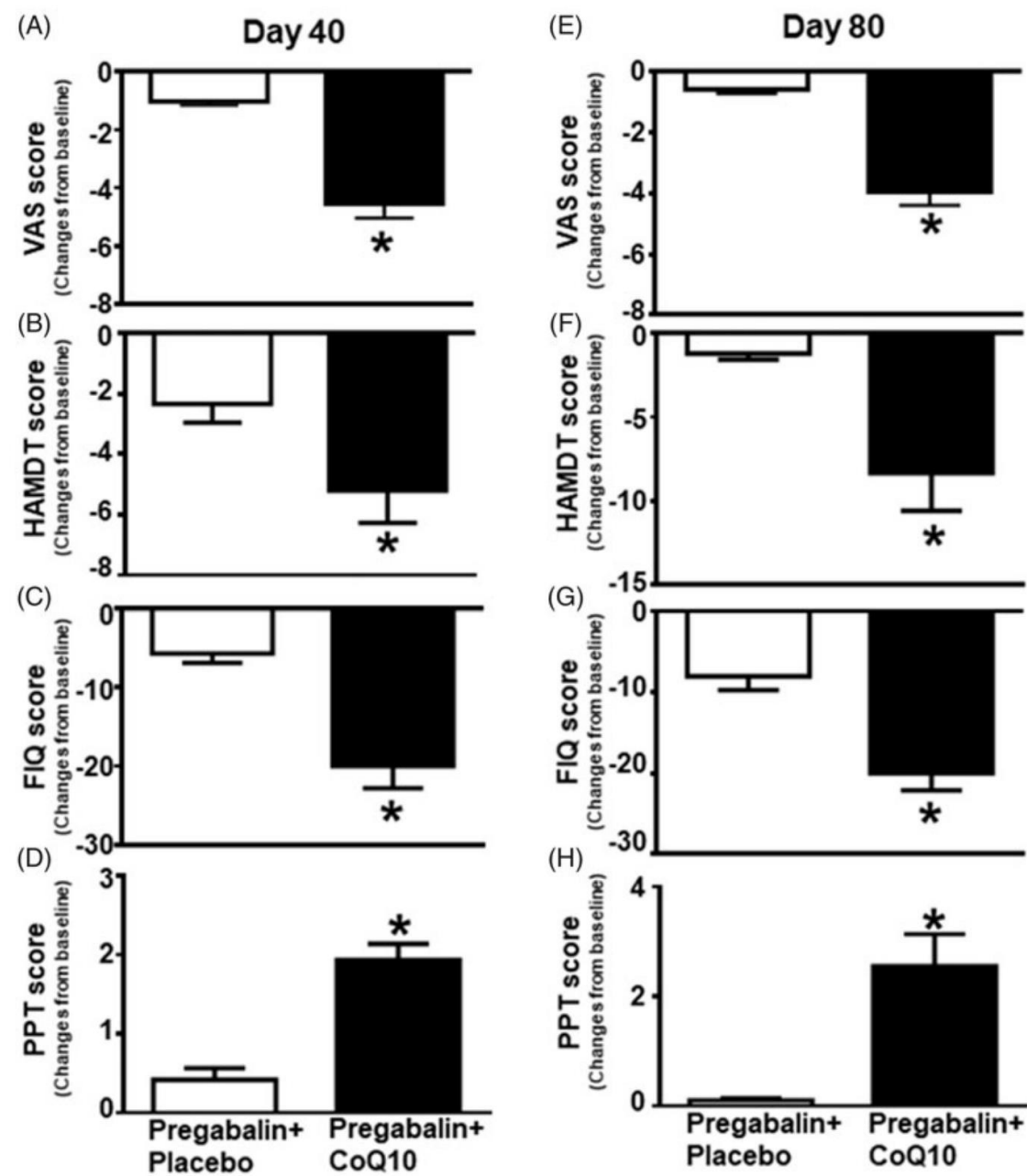


Figure 2. Changes from baseline in VAS, HAMDT, FIQ, and PPT scores at Day 40 and Day 80.

Research article | [Open access](#) | Published: 23 July 2014

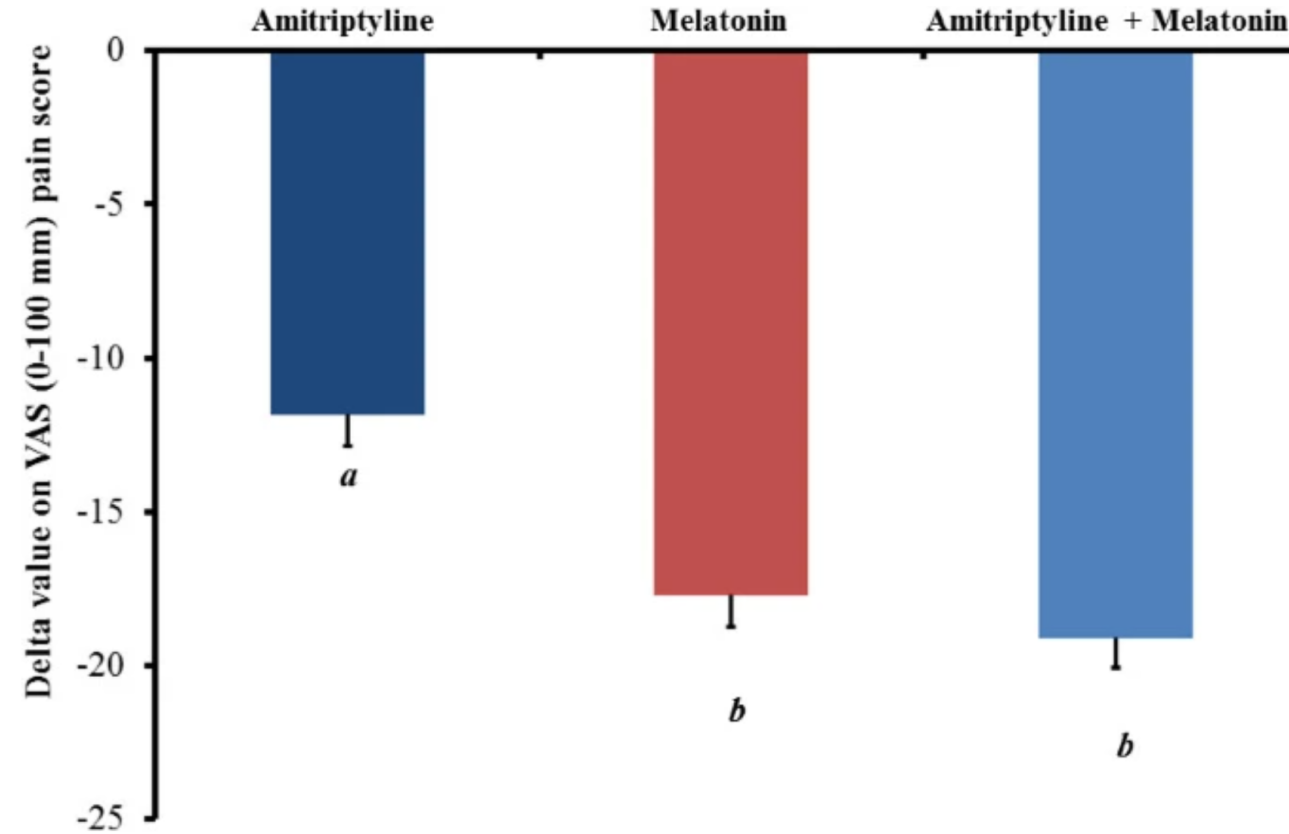
Melatonin analgesia is associated with improvement of the descending endogenous pain-modulating system in fibromyalgia: a phase II, randomized, double-dummy, controlled trial

[Simone Azevedo de Zanette](#), [Rafael Vercelino](#), [Gabriela Laste](#), [Joanna Ripoll Rozisky](#), [André Schwertner](#), [Caroline Buzzatti Machado](#), [Fernando Xavier](#), [Izabel Cristina Custódio de Souza](#), [Alicia Deitos](#), [Iraci L S Torres](#) & [Wolnei Caumo](#) 

[BMC Pharmacology and Toxicology](#) **15**, Article number: 40 (2014) | [Cite this article](#)

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Figure 2



Mean pain levels as Delta value (scores on VAS (0-100 mm) in last week of treatment minus scores one week pretreatment) in the three experimental groups. The error bars indicate the standard error of the mean. A letter *b* indicates a significant difference between the melatonin group and melatonin + amitriptyline groups compared with the amitriptyline group ($P < 0.05$). All comparisons were performed using a mixed analysis of variance (ANOVA) model, followed by the Bonferroni correction for *post hoc* multiple comparisons.

Randomized Controlled Trial

> Clin Exp Rheumatol. 2007 Mar-Apr;25(2):182-8.

Double-blind, multicenter trial comparing acetyl l-carnitine with placebo in the treatment of fibromyalgia patients

M Rossini ¹, O Di Munno, G Valentini, G Bianchi, G Biasi, E Cacace, D Malesci, G La Montagna, O Viapiana, S Adami

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PMID: 17543140

- *Fibromyalji hastalarında hiperaljezi ve mitokondriyal disfonksiyona ne yol açıyor olabilir?*

► [Biomedicines](#). 2024 Jul 11;12(7):1543. doi: [10.3390/biomedicines12071543](https://doi.org/10.3390/biomedicines12071543) [↗](#)

Fibromyalgia: A Review of the Pathophysiological Mechanisms and Multidisciplinary Treatment Strategies

[Lina Noelia Jurado-Priego](#)¹, [Cristina Cueto-Ureña](#)¹, [María Jesús Ramírez-Expósito](#)¹, [José Manuel Martínez-Martos](#)^{1,*}

Editor: Elena Lucarini¹

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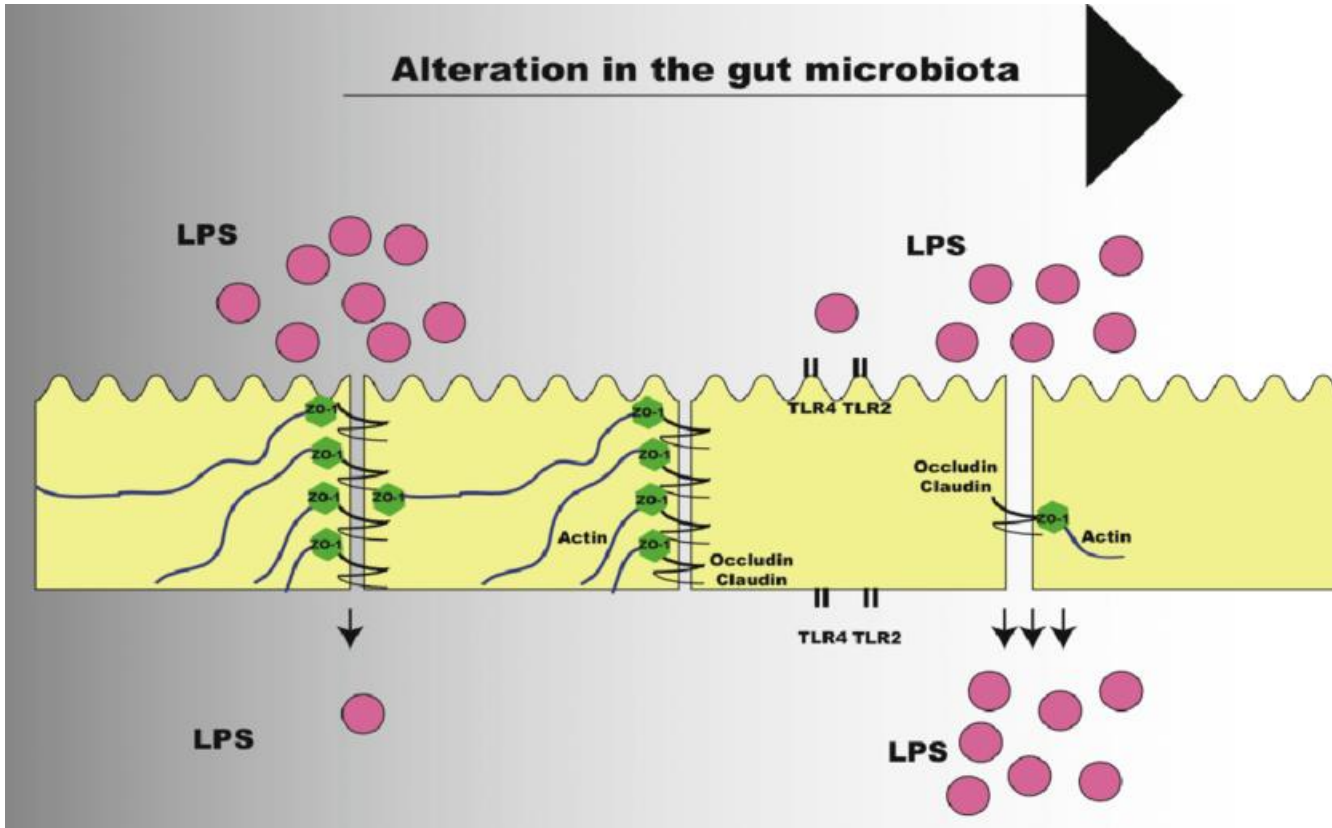
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Alteration in the gut microbiota



Randomized Controlled Trial > Brain Behav Immun. 2014 Oct;41:46-54.

doi: 10.1016/j.bbi.2014.05.001. Epub 2014 May 9.

Inflammation-induced hyperalgesia: effects of timing, dosage, and negative affect on somatic pain sensitivity in human experimental endotoxemia

Alexander Wegner¹, Sigrid Elsenbruch², Janina Maluck², Jan-Sebastian Grigoleit², Harald Engler², Marcus Jäger¹, Ingo Spreitzer³, Manfred Schedlowski², Sven Benson⁴

Affiliations + expand

PMID: 24814500 DOI: 10.1016/j.bbi.2014.05.001

- «Sonuçlarımız orta düzeyde bir **LPS** dozunun (0.8 ng/kg) **yaygın kas-iskelet hipersensitivitesi**, IL-6 artışı ve **negatif mizaca** yol açtığını gösteriyor»

Randomized Controlled Trial

> Pain. 2012 Apr;153(4):794-799. doi: 10.1016/j.pain.2011.12.001.

Epub 2012 Jan 20.

Acute experimental endotoxemia induces visceral hypersensitivity and altered pain evaluation in healthy humans

Sven Benson ¹, Joswin Kattoor, Alexander Wegner, Florian Hammes, Daniel Reidick, Jan-Sebastian Grigoleit, Harald Engler, Reiner Oberbeck, Manfred Schedlowski, Sigrid Elsenbruch

Affiliations + expand

PMID: 22264996 DOI: 10.1016/j.pain.2011.12.001

- **«Endotoksemi sağlıklı insanlarda visceral hipersensitivite ve bozulmuş ağrı algısına yol açıyor»**

Low rather than high dose lipopolysaccharide 'priming' of muscle provides an animal model of persistent elevated mechanical sensitivity for the study of chronic pain

Yoshiko Yamaguchi ¹, Tatsuyuki Hashimoto, Hiroki Sakurai, Takahiko Yoshimoto, Yusuke Ohmichi, Atsuko Morimoto, Kohei Harimoto, Mika Ohmichi, Kunihiro Eguchi, Takao Kumazawa

Affiliations + expand

PMID: 21306026 DOI: 10.1016/j.ejpain.2011.01.001

- Hayvan modellerinde ağrıya **kalıcı** duyarlılık **yüksek değil düşük doz LPS** ile kas uyarıldığında kronik ağrıya yol açacak biçimde ortaya çıkmış
- Yüksek doz LPS, beklendiği gibi akut inflamatuvar yanıtı açmış ancak kronik kalıcı ağrı gelişimi ile sonuçlanmamış
- «Yüksek doz LPS anti inflamatuvar mekanizmaları da uyararak bir negatif feed-back halkası ortaya çıkarmış olabilir. **Kronik düşük doz toksin ise bu kontrol mekanizmasının gelişmesine yol açmadan nörolojik ve inflamatuvar ağrı zeminini yaratıyor gibi görünüyor**»

➤ [Rheumatology \(Oxford\)](#). 2008 Aug;47(8):1223-7. doi: 10.1093/rheumatology/ken140.
Epub 2008 Jun 7.

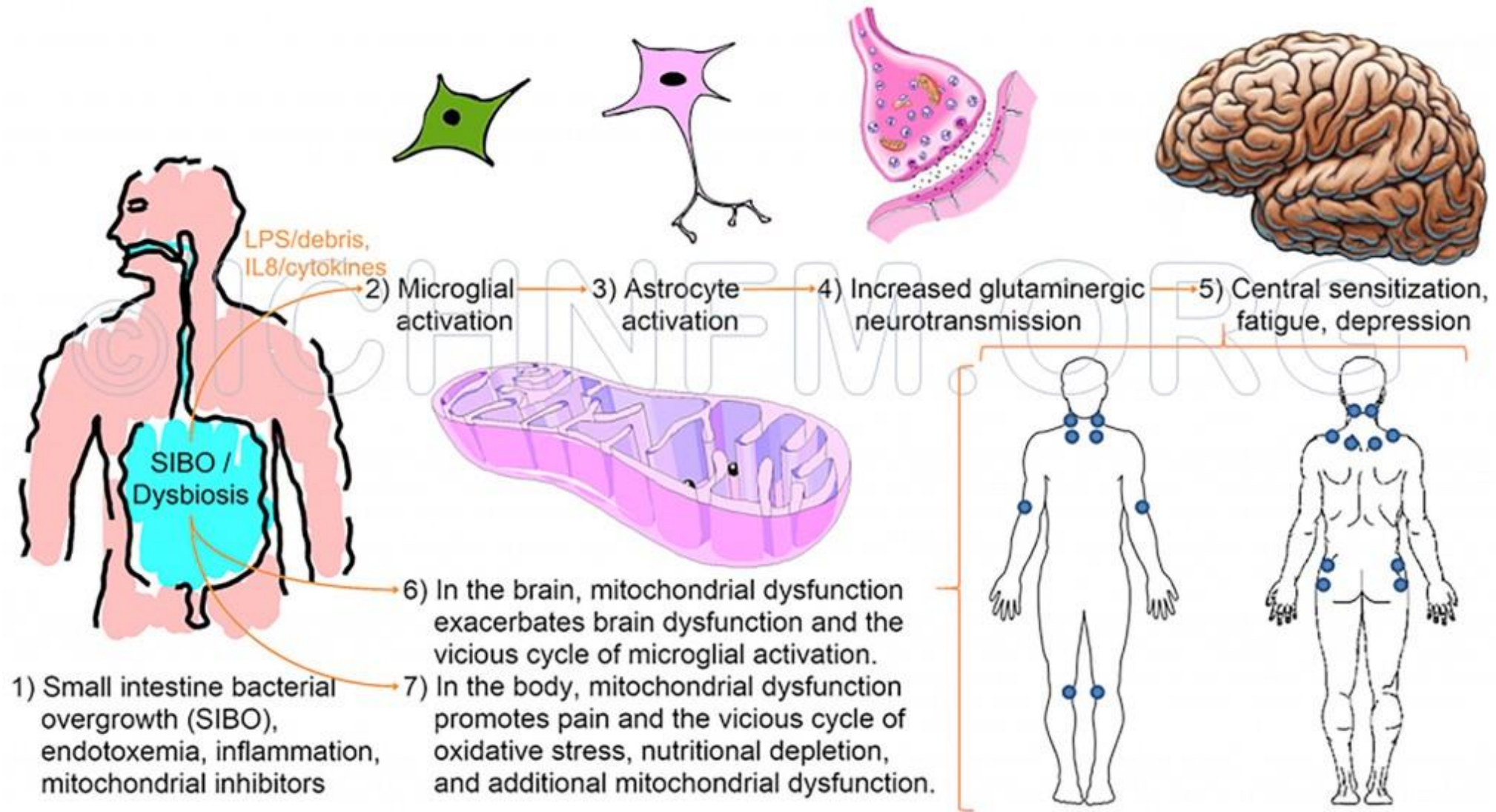
Altered intestinal permeability in patients with primary fibromyalgia and in patients with complex regional pain syndrome

A Goebel ¹, S Buhner, R Schedel, H Lochs, G Sprotte

- **«..permeability ($P < 0.0003$, for the three groups)»**

- Amerikan Romatoloji Derneği hasta bilgilendirme sayfasından:
- *«Fibromyaljili kişinin beyinde ağrı işleyen merkezlerde «volüm kontrol düğmesi» biraz fazla açık gibi görünüyor»*

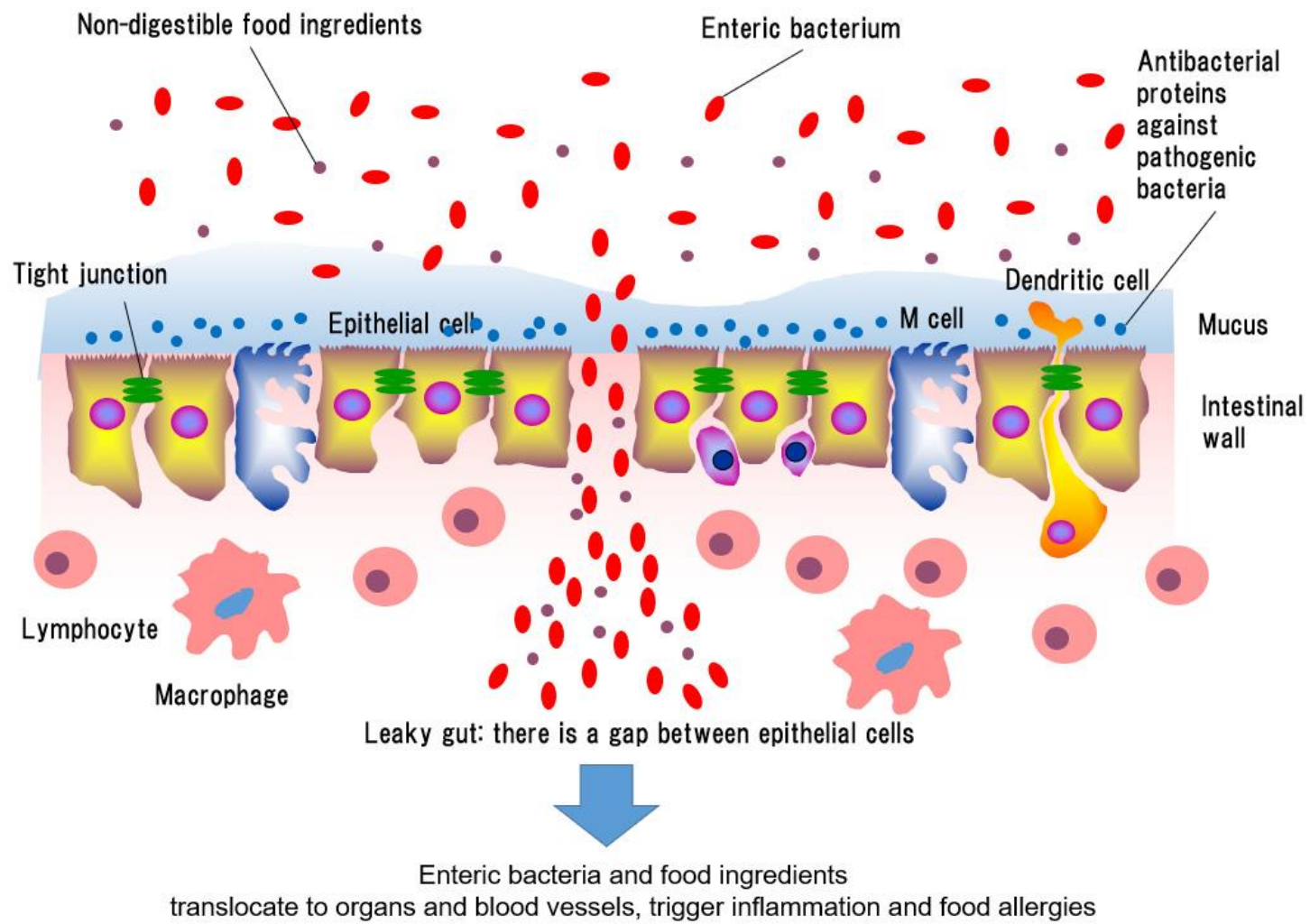
- *Fibromyalji hastalarında hiperaljezi ve mitokondriyal disfonksiyona ne yol açıyor olabilir?*



[J Gastroenterol Hepatol](#). 2017 Apr;32(4):828-836. doi: 10.1111/jgh.13588.

Colonic N-methyl-d-aspartate receptor contributes to visceral hypersensitivity in irritable bowel syndrome.

Qi Q¹, Chen F¹, Zhang W¹, Wang P¹, Li Y¹, Zuo X¹.



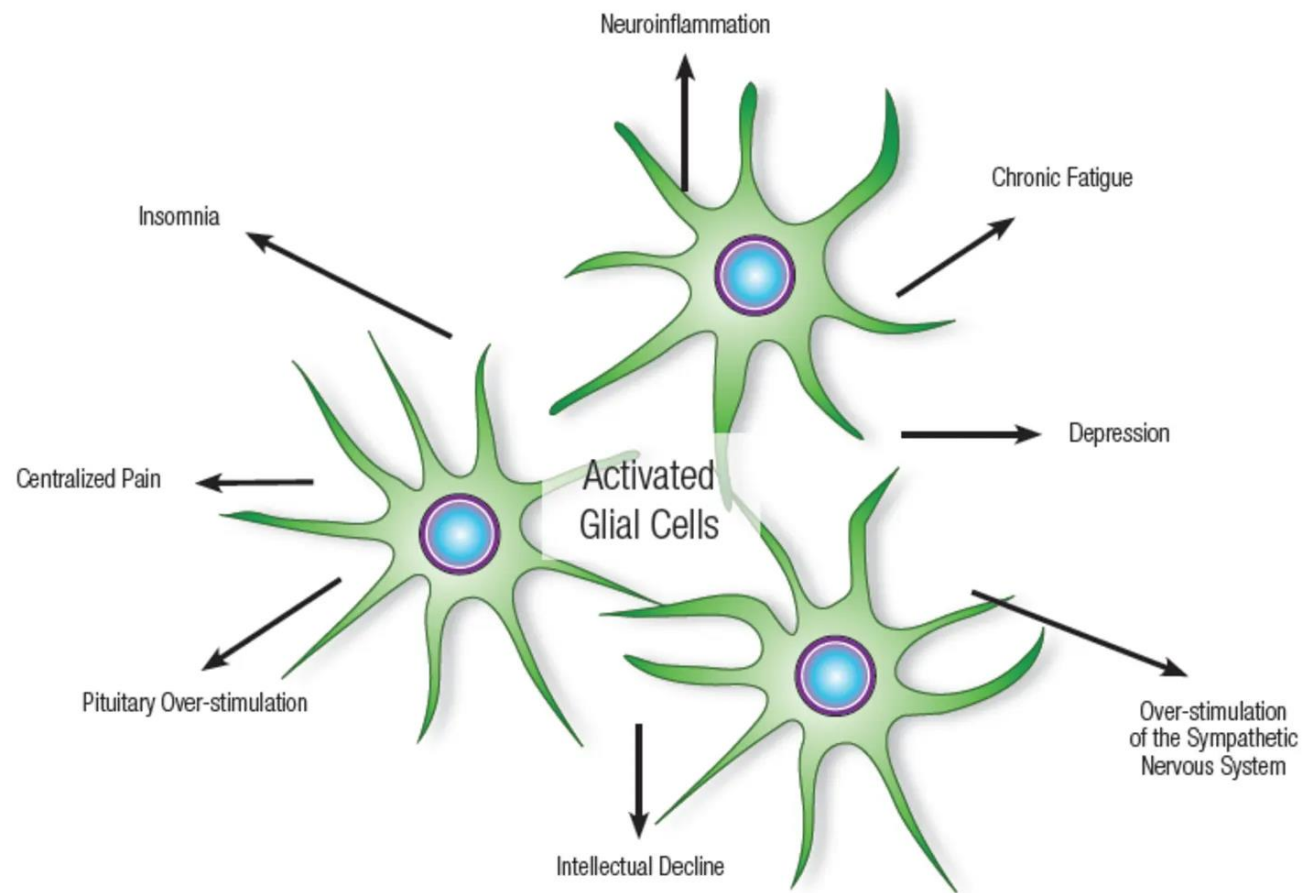


Table 1. Four Basic Types of Glial Cells

Name	Basic Function
Microglia	Macrophage-like cells that remove waste and microorganisms and, thus, function in immunity and inflammation
Astrocyte	Involved in the physical structure of the brain (formation of synapses) and the storage and distribution of energy sources; also may be involved with long-term memory
Oligodendrocyte	Support and insulate neurons; the myelinating cells of the CNS
Schwann cell	Produce myelin sheaths for neurons in the peripheral nervous system

CNS, central nervous system

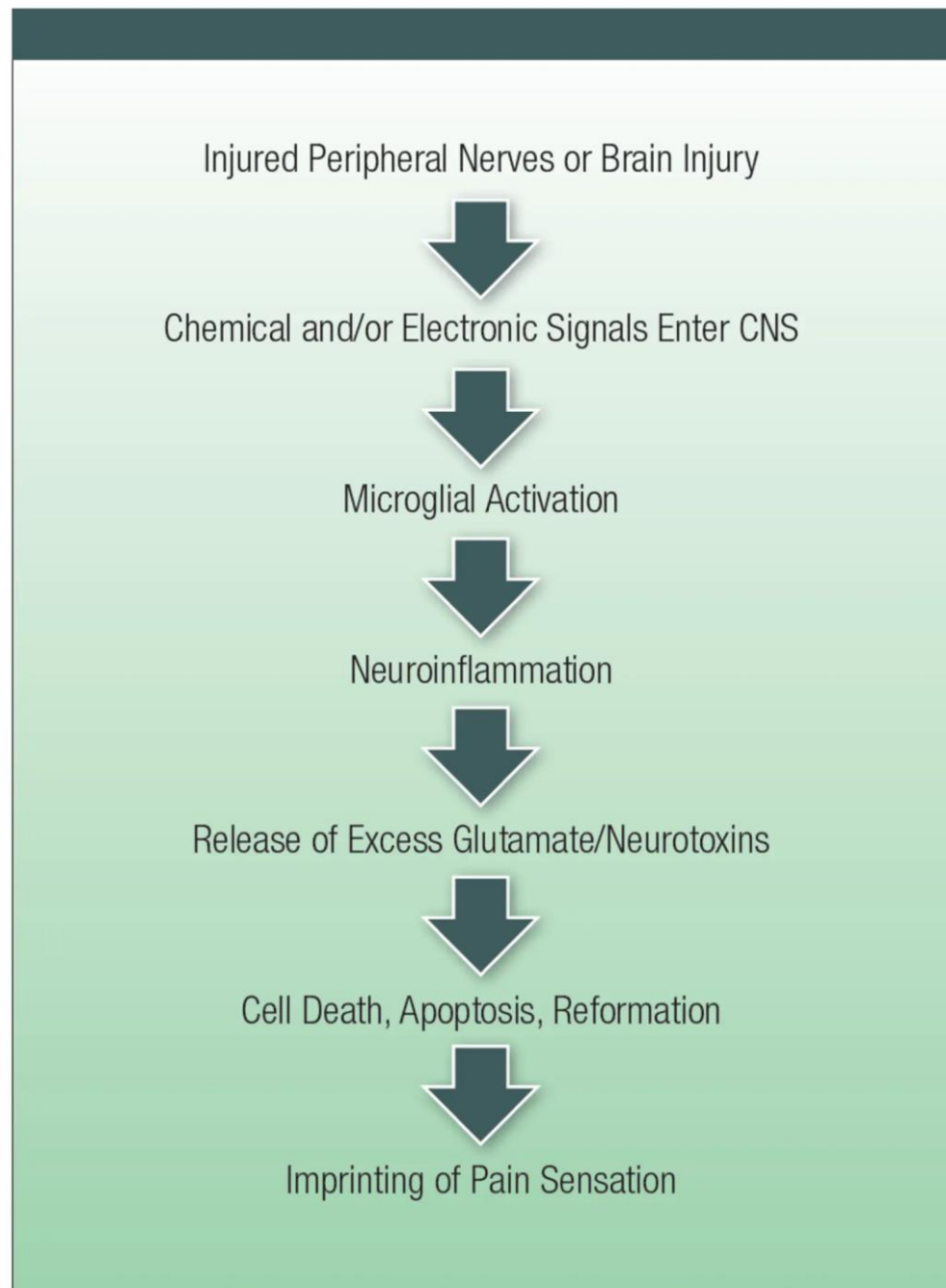


Figure 1. Algorithm illustrating how centralized pain develops.
CNS, central nervous system

Consequences of the Inflamed Brain

[S. Maier](#), [L. Watkins](#) • Published 2012 • Medicine

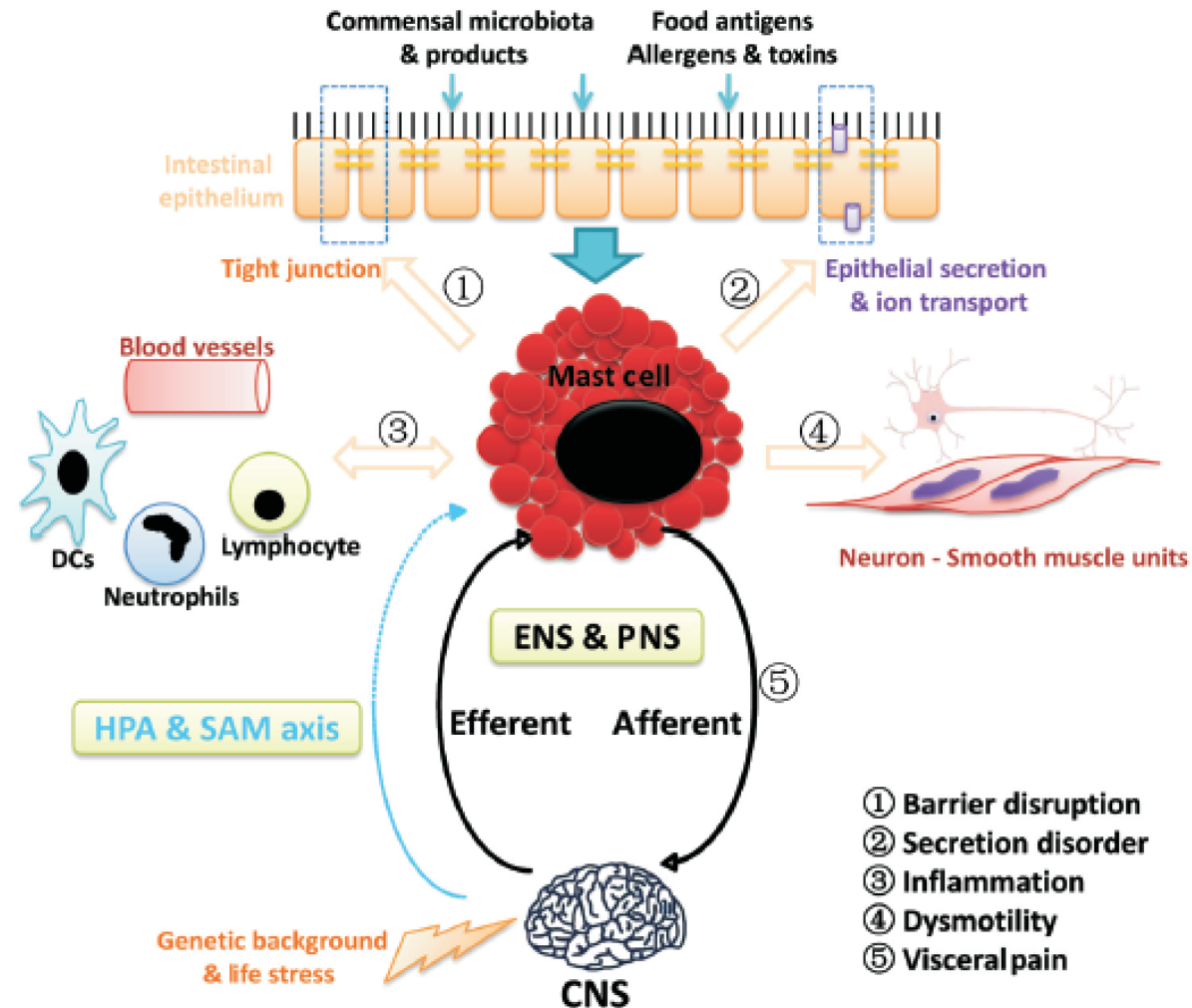
TLDR New research has led to important advances in understanding of how immune-related events in the periphery can influence CNS processes, thereby altering cognition, mood, and behavior, and these advances are suggesting that inflammation may have important long term implications for the brain.

Glial aktivasyon →

- Düşük fizik aktivite
- İştahsızlık
- Sosyal aktiviteden uzaklaşma
- Libido yokluğu
- Depresyon
- Hafıza zayıflaması
- Ağrı duyarlılığında artış

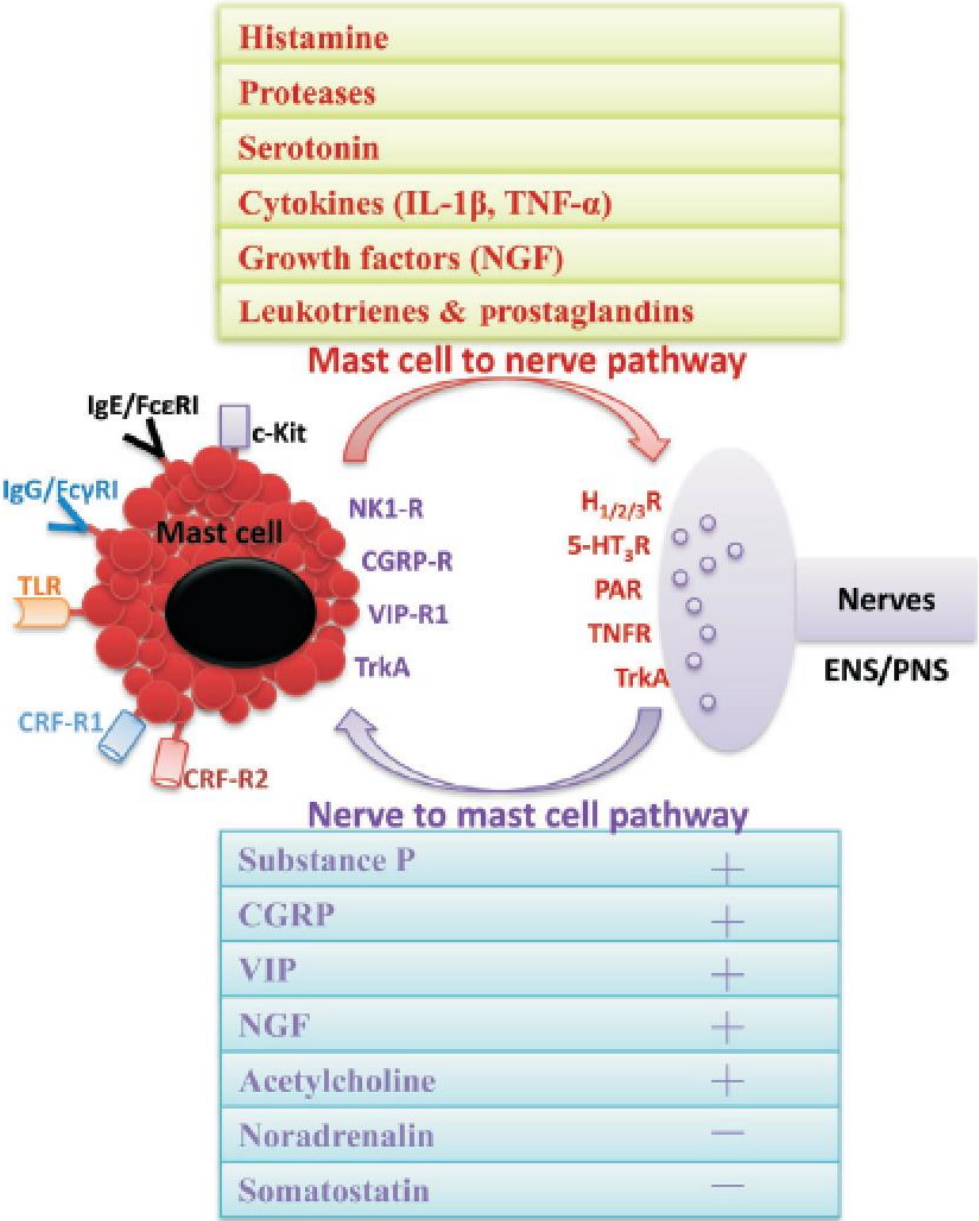
Mast Cells and Irritable Bowel Syndrome: From the Bench to the Bedside

Lei Zhang¹, Jun Song¹, Xiaohua Hou¹



Mast cell involvement in interstitial cystitis: a review of human and experimental evidence ☆

Theoharis C Theoharides ^{a b} ✉, Duraisamy Kempuraj ^a, Grannum R Sant ^c



> [J Pain](#). 2011 Apr;12(4):436-43. doi: 10.1016/j.jpain.2010.10.003. Epub 2010 Dec 13.

Gray matter volumes of pain-related brain areas are decreased in fibromyalgia syndrome

[Michael E Robinson](#)¹, [Jason G Craggs](#), [Donald D Price](#), [William M Perlstein](#), [Roland Staud](#)

Affiliations — collapse

Affiliation

- ¹ Department of Clinical and Health Psychology, McKnight Brain Institute, University of Florida College of Medicine, Gainesville, FL 32610-0221, USA.

► J Neurosci. 2007 Apr 11;27(15):4004–4007. doi: [10.1523/JNEUROSCI.0098-07.2007](https://doi.org/10.1523/JNEUROSCI.0098-07.2007) 

Accelerated Brain Gray Matter Loss in Fibromyalgia Patients: Premature Aging of the Brain?

[Anil Kuchinad](#)^{1,2}, [Petra Schweinhardt](#)¹, [David A Seminowicz](#)¹, [Patrick B Wood](#)¹, [Boris A Chizh](#)⁴, [M Catherine Bushnell](#)^{1,2,3}, 

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- «Çalışmamızda fibromyaljili hastalarda **beyin gri maddesinin** anlamlı olarak **azalmış** olduğunu ve yaşa bağlı gri madde **kaybının daha hızlı** olduğunu gördük. FM süresi uzadıkça bu kayıp daha fazla idi ve **her FM yılı için normal yaşılanmanın 9.5 katına** ulaştığını saptadık»

Chronic back pain is associated with decreased prefrontal and thalamic gray matter density

A Vania Apkarian¹, Yamaya Sosa, Sreepadma Sonty, Robert M Levy, R Norman Harden, Todd B Parrish, Darren R Gitelman

Affiliations — collapse

- *Kronik bel ağrısı olan kişilerde beyin gri madde volümü sağlıklı kişilere göre %5-11 daha düşük. Bu azalma 10-20 yıllık normal yaşlanmaya karşılık gelecek boyutta*
- *Volüm kaybı **ağrının süresi** ile ilişkili. Kronik ağrılı geçen her yıla karşılık gri maddede 1.3 cm³ kayıp ortaya çıkıyor*

Leaky Gut / SIBO → Düşük dozda LPS ve diğer toksinlerin (H₂S vd) sisteme girişi→

SSS'de glial aktivasyon → Astrosit aktivasyonu → NMDA reseptörlerinin aşırı uyarılması ile glutaminerjik stimulasyon → **Santral sensitizasyon**

LPS ve inflamatuvar sitokinler → HPA aksı disfonksiyonu: **Depresyon/ Anksiyete**

LPS ve inflamatuvar sitokinler → Serbest radikaller, oksidatif stres ve **Mitokondriyal disfonksiyon**