



The Impact of Caffeine Intake on Patients with Systemic Lupus Erythematosus: Protect Yourself, Drink More Coffee!

Valeria Orefice¹ , Fulvia Ceccarelli¹ , Cristiana Barbati¹ , Carlo Perricone² , Cristiano Alessandri¹ , Fabrizio Conti¹ 

¹Lupus Clinic, Dipartimento di Scienze Cliniche, Internistiche, Anestesiologiche e Cardiovascolari, Sapienza Università di Roma, Rome, Italy, ²Reumatologia, Dipartimento di Medicina e Chirurgia, Università di Perugia, Perugia, Italy

Article Submitted: 15 Oct 2020; Revised Form: 1 Nov 2020; Article Accepted: 2 Nov 2020; Available Online:

Systemic lupus erythematosus (SLE) is an autoimmune disease mainly affecting mostly young women, potentially involving any organ/system. The central role of environmental factors in disease pathogenesis has been widely demonstrated: among these, an emerging interest has been pointed to dietary factors.¹⁻⁴ In this context, the spectrum of research on caffeine, one of the most widely consumed products in the world, is exponentially growing during the last decade. Indeed, caffeine, acting as a non-specific phosphodiesterase inhibitor, seems to be able to interact with multiple components of the immune system, influencing both innate and adaptive response.⁵⁻⁸

Recently, we performed a study to evaluate the impact of caffeine intake on SLE activity and phenotype.⁹ By analysing a large monocentric cohort, we identified an inverse correlation between caffeine consumption and disease activity, in terms of SLEDAI-2k values and serum cytokines levels.⁹ Our results suggest that a moderate caffeine intake could modulate disease activity, and thus influence chronic damage. Indeed, we were able to demonstrate that lower caffeine intake was associated

with more frequent major organ involvement - such as renal and neuropsychiatric manifestations - and anti-dsDNA positivity.

Our results are concordant with a previous published study evaluating a Colombian SLE cohort, in which coffee consumption was

positively associated with 6 months clinical remission.¹⁰ Moreover, Kiyohara and colleagues analysed the association between coffee intake and SLE risk, demonstrating only a marginal dose-dependent association.¹¹

Several studies were published so far about the contribution of diet in SLE aetiopathogenesis, suggesting a possible influence on systemic inflammatory status, leading to modifications on inflammatory cell activity and cytokine levels.¹² Taken together, data available from the literature suggest that a diet rich in vitamin D and A, polyunsaturated fatty acids, and phenols could be able to reduce the inflammatory burden.¹² Furthermore, a protective role of the traditional Mediterranean diet and a low-sodium dietary regimen has been recently suggested.¹³ We added new information about the relationship between caffeine and SLE; in fact, despite the worldwide spread of caffeine usage, very few data on SLE have been published so far.

Furthermore, our study provided deeper evidence on the role of caffeine on disease activity, by identifying an inverse correlation between daily caffeine intake and inflammatory cytokine levels. Indeed, for the first time, we demonstrated significantly lower serum levels of IFN γ , IFN α , IL-17, and IL-6 in SLE patients with higher daily caffeine intake.⁹ In this regard, Iris and colleagues demonstrated that *in vitro* dose-dependent treatment with caffeine could downregulate mRNA levels of key inflammation-related genes in peripheral blood mononuclear cells of healthy donors, and similarly, decrease levels of different inflammatory cytokines in a dose-dependent way.¹⁴

In conclusion, in the last years, a growing interest has focused on the role of caffeine in the immune-related diseases pathogenesis and phenotype. In particular, *in*

Corresponding Author:

Carlo Perricone
Reumatologia, Dipartimento di Medicina
e Chirurgia
Università di Perugia
P.le Menghini, 1
06129, Perugia, Italy
Tel.: +39 0755783573
E-mail: carlo.perricone@gmail.com

vitro and *in vivo* studies suggest a possible immunoregulatory dose-dependent effect exerted through the modulation of several serum cytokine levels; in the same way, caffeine could influence SLE phenotype favouring less severe disease manifestations.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Kaul A, Gordon C, Crow MK, Touma Z, Urowitz MB, van Vollenhoven R, et al. Systemic lupus erythematosus. *Nat Rev Dis Primers* 2016;16:16039.
2. Perricone C, Ciccacci C, Ceccarelli F, Di Fusco D, Spinelli FR, Cipriano E, et al. TRAF3IP2 gene and systemic lupus erythematosus: association with disease susceptibility and pericarditis development. *Immunogenetics* 2013;65:703-9.
3. Ceccarelli F, Perricone C, Borgiani P, Ciccacci C, Rufini S, Cipriano E, et al. Genetic factors in systemic lupus erythematosus: contribution to disease phenotype. *J Immunol Res* 2015;2015:745647.
4. Tsokos GC, Lo MS, Reis PC, Sullivan KE. New insights into the immunopathogenesis of systemic lupus erythematosus. *Nat Rev Rheumatol* 2016;12:716-30.
5. Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, et al. Caffeine therapy for apnea of prematurity. *N Engl J Med* 2006;354:2112-21.
6. Fione G, Borgkvist A, Uziello A. Caffeine as a psychomotor stimulant: mechanism of action. *Cell Mol Life Sci* 2004;61:857-72.
7. Aronsen L, Orvoll E, Lysaa R, Ravna AW, Sager G. Modulation of high affinity ATP-dependent cyclic nucleotide transporters by specific and non-specific cyclic nucleotide phosphodiesterase inhibitors. *Eur J Pharmacol* 2014;745:249-53.
8. Al Reef T, Ghanem E. Caffeine: well-known as psychotropic substance, but little as immunomodulator. *Immunobiology* 2018;818-25.
9. Orefice V, Ceccarelli F, Barbati C, Lucchetti R, Olivieri G, Cipriano E, et al. Caffeine intake influences disease activity and clinical phenotype in systemic lupus erythematosus patients. *Lupus* 2020 Oct;29(11):1377-84.
10. Alzate MA, Ochoa F, Ortiz-Salazar P, Hernandez-Parra D, Pineda R. 353 Coffee consumption and clinical outcomes in Colombian patients with systemic lupus erythematosus. *Lupus Sci Med* 2017;4.
11. Kiyohara C, Washio M, Horiuchi T, Asami T, Ide S, Atsumi T, et al. Modifying effect of N-acetyltransferase 2 genotype on the association between systemic lupus erythematosus and consumption of alcohol and caffeine-rich beverages. *Arthritis Care Res (Hoboken)* 2014;66:1048-56.
12. Aparicio-Soto M, Sanchez-Hidalgo M, Alarcon-de-la-Lastra C. An update on diet and nutritional factors in systemic lupus erythematosus management. *Nutr Res Rev* 2017;30:118-37.
13. Scrivo R, Massaro L, Barbati C, Vomero M, Ceccarelli F, Spinelli FR, et al. The role of dietary sodium intake on the modulation of T helper 17 cells and regulatory T cells in patients with rheumatoid arthritis and systemic lupus erythematosus. *PLoS One* 2017;12:e0184449.
14. Iris M, Tsoua P, Sawalha A. Caffeine inhibits STAT1 signaling and downregulates inflammatory pathways involved in autoimmunity. *Clin Immunol* 2018;192:68-77.