3rd BIOPHARM SCIENTIFIC ANNUAL MEETING
BSAM3, Alger le 16 Mars 2023

In-vitro effects of nicotine on nitric oxide, interleukin 1β and interleukin 37 production by human peripheral blood mononuclear cells (PBMC) from patients with Behçet disease: a promising anti-inflammatory therapeutic tool

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Abstract : Behçet's disease is a chronic systemic inflammatory disorder associated with a cytokine profile disruption and increased nitric oxide levels. In our current study we sought to evaluate the *in-vitro* modulatory effect of nicotine, the principal alkaloid of tobacco, on nitric oxide (NO), interleukin 1β (IL-1β) and interleukin 37 (IL-37) production during Behçet's disease. Peripheral blood mononuclear cells cultures were performed with or without nicotine (200 µg/ml). Culture supernatants were harvested after 24 h of incubation. NO, IL-1β and IL-37 measurements were, respectively, performed by modified Griess method and ELISA sandwich. Our results showed that nicotine significantly reduced NO and IL-1β levels in patients with Behçet's disease, while it increased IL-37 production. Our results showed no sex differences in the effects of nicotine on the production of nitric oxide and IL-1β nor IL-37 in PBMC of patients. Our findings suggest that nicotine may provide a potential therapeutic strategy targeting inflammation during Behçet's disease.

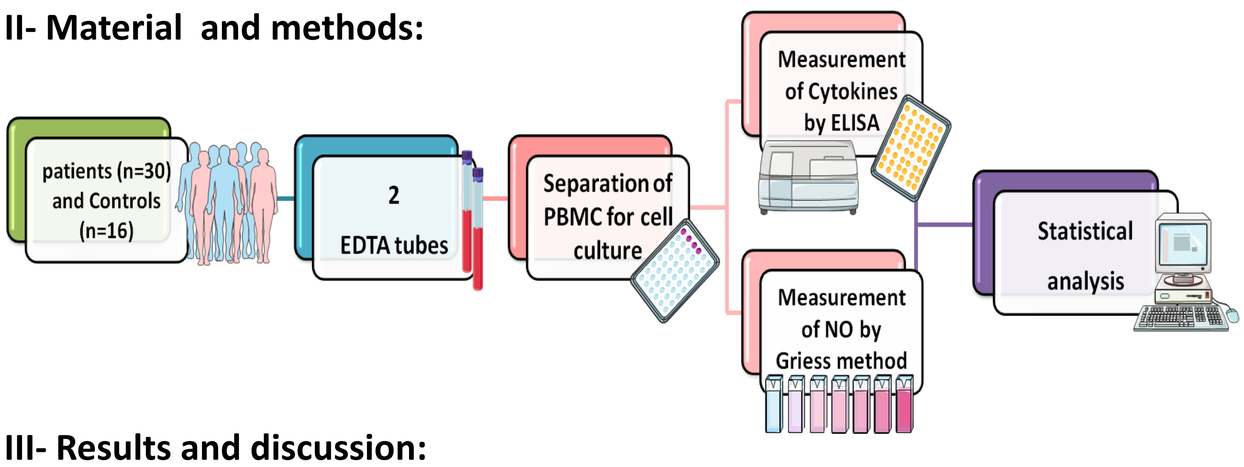
Key words: Behçet disease, Nicotine, nitric oxide, Cytokines, anti-inflammatory effect

I- Introduction :

Behcet's disease (BD) is a multisystemic vasculitis of uncertain etiology. At a crossroad between autoimmune and auto-inflammatory disorders, it is characterized by a chronic evolution marked by acute inflammations, separated by remission phases. Activated innate immunity plays an important role in the pathogenesis of BD with an overproduction of inflammatory parameters by innate immune cells such as macrophages, neutrophiles, natural killers and dendritic cells, may cause a higher production of cytokines and nitric oxide (NO).

As Behçet's disease is an inflammatory disorder, the goal of treatment is therefore based on modulation of inflammation. Several recent studies have reported the immunomodulatory effects of nicotine on the production of different pro-inflammatory cytokines. Despite all studies on nicotine, the direct effect on peripheral blood mononuclear cells (PBMC) in Behçet's disease and on IL-37 production has not yet been studied. Our study was conducted with this in mind

II- Material and methods:



III- Results and discussion:

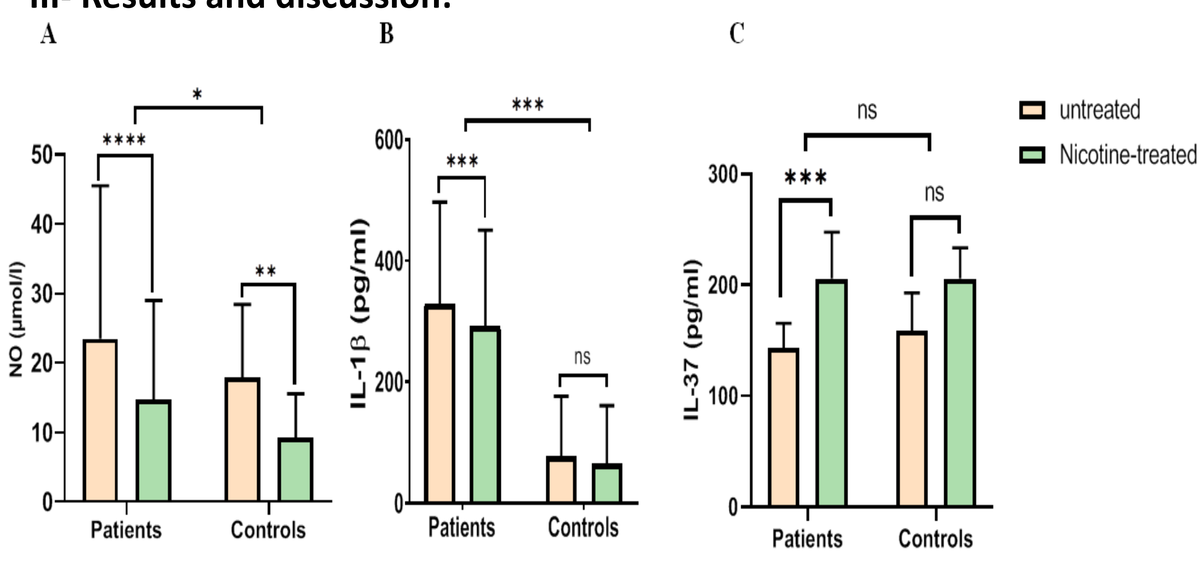


Figure 1: Effect of nicotine on NO (A), IL-1β (B) and IL-37 (C) by ELISA in patients and healthy controls .

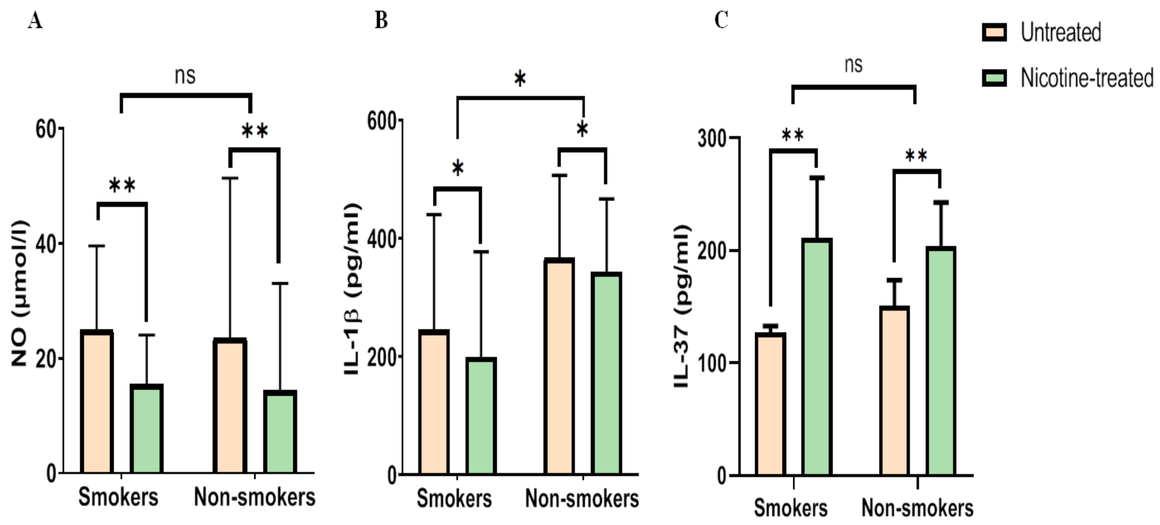


Figure 2: Effect of nicotine on in-vitro production of NO (A), IL-1β (B) and IL-37(C) by PBMC in smokers and non-smokers patients with BD.

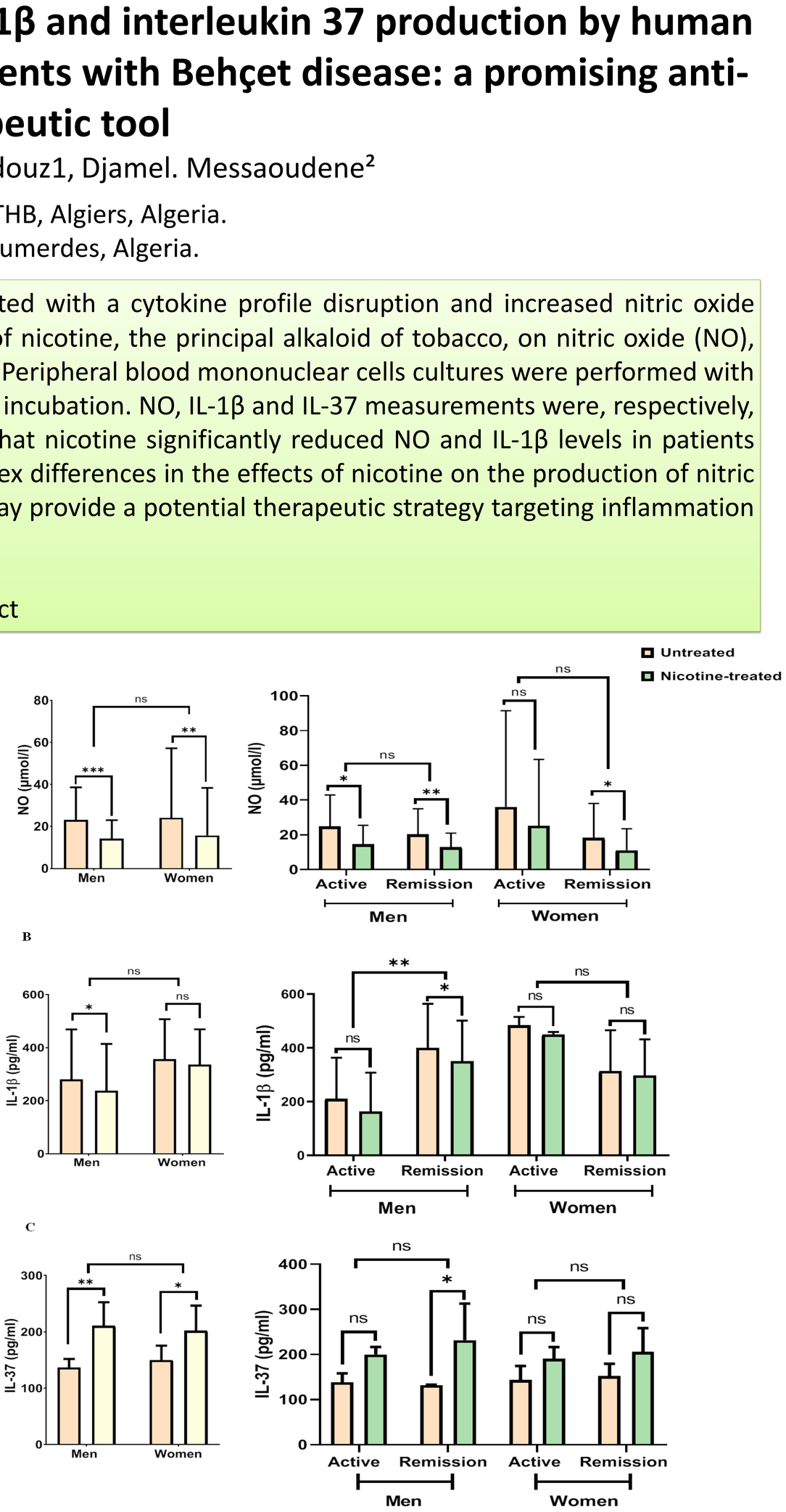


Figure 3: Effect of nicotine on NO (A), IL-1β (B) and IL-37(C) of Women and Men in active and remission phase of BD.

In our study, it was clearly shown that nicotine treatment decreased the production of both IL-1β and nitric oxide by the PBMC of BD patients while it increased IL-37 levels.

Interestingly, Our data showed that PBMC of smokers and non-smokers responded significantly to the nicotine treatment. Although, ANOVA test indicated that IL-1β decreased production was related to the *in-vivo* presence of nicotine which suggests that IL-1β may require a long term treatment, while the *in-vitro* nicotine treatment was enough to effect NO production.

Importantly, in our current study, nicotine has significantly reduced the production of nitric oxide by PBMC in both active and remission phase; this reduction was more pronounced in remission stage. Although the suppressive effect on IL-1β production was noticed only in remission phase, no differences were observed in patients in the active phase. This effect could be explained by the high level of immune activation during active stage. It would seem that this level could not be sufficiently controlled by nicotine. In accordance with this hypothesis, the observed augmentation in IL-37 in both phases was also more pronounced in remission. Moreover, ANOVA analysis showed no significant differences between both sexes, suggesting that nicotine can affect IL-1β, NO and IL-37 production in both men and women.

Conclusion: Our data report that nicotine reduced NO and IL-1β levels in patients with Behçet's disease, while it increased IL-37 production. Results showed no sex differences responding to the treatment. The obtained results indicate that pure nicotine has beneficial effects and could constitute a promising therapeutic approach during Behçet's disease.

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