Non-Severe Preeclampsia and Subclinical Inflammation: A Study of Cyclophilin A, NF-κB, PARP- 1, and Apoptosis in Human Placentas

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Abstract

Objective: To compare the expression of CyP-A, NF-κB, PARP-1, and apoptotic index in Non-Severe Preeclampsia (NS-PE) and Normal Pregnancy (NP) and explore their roles in inflammation during preeclampsia.

Methods: Conducted in Depok, Indonesia, the cross-sectional study involved 28 participants divided into NS-PE and NP groups based on ISSHP criteria. NP was defined as uncomplicated pregnancies at 38–40 weeks gestation. Placental weight was measured, and ELISA was used to assess biomolecule levels. Data were analyzed using T-tests or Mann-Whitney tests.

Result: Maternal gestational age, body mass index, and leukocyte levels were significantly higher in NS-PE. The apoptotic index, measured by TUNEL assay, was also significantly elevated in NS-PE (41.56 ±24.87) compared to NP (23.96 ±18.79; p = 0.044). While CyP-A, PARP-1, and NF-κB levels were higher in NS-PE eventhough they were not statistically significant. Immunohistochemistry confirmed an overall increase in these molecules, supporting their clinical relevance.

Conclusion: Despite the lack of statistical significance, increased inflammation and apoptosis in NS-PE may contribute to placental dysfunction and adverse pregnancy outcomes.

Key words: Apoptosis; inflammation; preeclampsia.

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Non-Severe Preeclampsia dan Inflamasi Subklinis: Studi CyP-A, NF-κB, PARP-1, dan Apoptosis pada Plasenta Manusia

Abstrak

Tujuan: Penelitian ini bertujuan untuk mengetahui perbedaan ekspresi CyP-A, NF-κB, PARP-1, dan indeks apoptosis antara preeklamsia *non-severe* (NS-PE) dan kehamilan normal (NP), serta perannya dalam proses inflamasi pada preeklamsia.

Metode: Metode penelitian yang digunakan dalam penelitian ini adalah *cross-sectional*. Penelitian ini dilakukan di Depok, Indonesia, dengan 28 partisipan yang dikelompokkan menjadi NS-PE dan NP berdasarkan kriteria ISSHP. Berat plasenta diukur dan kadar biomolekul dianalisis menggunakan ELISA. Uji T dan alternatif Mann-Whitney digunakan untuk analisis statistik.

Hasil: Hasil penelitian menunjukkan bahwa usia kehamilan, indeks massa tubuh (IMT), dan kadar leukosit secara signifikan lebih tinggi pada NS-PE. Indeks apoptosis (TUNEL) juga lebih tinggi secara signifikan pada NS-PE (41,56 ±24,87) dibandingkan NP (23,96 ±18,79; p = 0,044). Kadar CyP-A, PARP-1, dan NF-κB lebih tinggi pada NS-PE meskipun tidak signifikan secara statistik, pemeriksaan IHK mengonfirmasi relevansi klinis peningkatan pada keseluruhan biomolekul tersebut.

Kesimpulan: Meskipun signifikansi statistik rendah, peningkatan peradangan dan apoptosis pada NS-PE dapat menyebabkan disfungsi plasenta dan dampak buruk pada kehamilan.

Kata kunci: Apoptosis; inflamasi; preeklamsia.

Introduction

Preeclampsia (PE) is a major hypertensive disorder of pregnancy and one of the great obstetrical syndromes, contributing significantly to maternal, fetal, and neonatal morbidity and mortality worldwide.[1, 2] Women with PE face a 30% increased risk of developing long-term cardiovascular diseases, including hypertension within a decade postpartum, while infants born to mothers with PE exhibit a heightened risk of future cardiovascular complications.[3] Despite extensive research, the pathophysiological mechanisms underlying PE remain incompletely understood, with growing evidence highlighting the critical role of inflammation in disease progression.

A key feature of PE is poor placental perfusion, which triggers a complex cascade of inflammatory responses. Cyclophilin A (CyP-A), a potent proinflammatory mediator, plays a pivotal role in this cascade by facilitating intercellular communication under conditions of oxidative stress, infection, and hypoxia.[4] Once secreted extracellularly, CyP-A binds to Cluster of Differentiation 147 (CD147), initiating an inflammatory response that promotes cytokine production, endothelial dysfunction, and myocardial remodeling.[5] These inflammatory changes contribute to cardiovascular pathology and further exacerbate placental dysfunction. Notably, CyP-A also activates nuclear factor kappa B (NF-κB), a central regulator of immune and inflammatory pathways in PE.

NF-κB is excessively activated in PE due to persistent placental hypoxia and oxidative stress, leading to increased proinflammatory cytokine secretion, impaired trophoblast invasion, and endothelial dysfunction, all of which contribute to hypertension and placental insufficiency.[6, 7] This excessive activation of NF-κB further amplifies the inflammatory response and perpetuates the disease cycle. Poly (ADP-ribose) polymerase-1 (PARP-1), a nuclear protein, serves as a transcriptional coregulator within the NF-κB pathway and plays a crucial role in modulating inflammatory responses.[8, 9] PARP-1 influences chromatin remodeling and facilitates the recruitment of transcriptional machinery to NF-κB target genes. However, excessive activation of PARP-1 can lead to NAD+ depletion, thus contributing to tissue damage in chronic inflammatory states.[8]

Although the inflammatory cascade in PE is multifaceted and not fully elucidated, evaluating a pathway and confirming apoptotic activity provides valuable insight into disease pathology. The apoptotic index, as assessed through TUNEL assays, serves as an important indicator of trophoblast cell turnover and placental integrity in PE.[10, 11] Increased apoptosis in the placenta has been associated with impaired trophoblast invasion, leading to compromised placental function and disease progression.[12] Investigating inflammatory mediators may provide a more comprehensive understanding of PE pathogenesis.

Despite increasing evidence of the involvement of CyP-A, NF-κB, PARP-1, and apoptosis in PE, studies examining these factors collectively in human placental tissue remain limited. Therefore, this study aims to compare the expression of CyP-A, NF-κB, PARP-1, and apoptotic index in Non-Severe Preeclampsia (NS-PE) and Normal Pregnancy (NP) to elucidate their roles in the inflammatory cascade of PE. By identifying key molecular interactions within this pathway, this research may contribute to improved diagnostic and therapeutic strategies for PE.

Method

We conducted a cross-sectional study with 28 participants, calculated based on a two-sided comparison of two mean population hypothesis tests (α=5% and β=20%). We

collected data at the General Hospital in Depok, Indonesia, over five consecutive months (October 2018 to March 2019). Participants were categorized into two groups: non-severe preeclampsia (NS-PE) and normal pregnancy (NP). The study was approved by the Faculty of Medicine, Universitas Indonesia (0384/UN2.F1/ETIK/2018).

Preeclampsia was defined based on International Society for the Study of Hypertension in Pregnancy (ISSHP).[1] We categorized pregnancies without complications at 38-40 weeks gestation as NP. We excluded pregnancies with heart disease, autoimmune disease, congenital abnormalities, preterm labor, HELLP syndrome, and non-obstetric complications such as heart failure, stroke, renal failure, and liver failure. The remaining participants were classified as non-severe preeclampsia (NS-PE).

We identified maternal and fetal characteristics, cardiovascular function indices, and biomolecules. Maternal characteristics included age, gestational age, BMI, body surface area, gravida, and parity. Fetal characteristics included birth weight and placental weight. Cardiovascular indices included systolic and diastolic blood pressure (sphygmomanometer), heart rate, cardiac output, cardiac index, and total peripheral resistance (TPR) (echocardiography), maternal-fetal ultrasound (GE Voluson machine) operated by obstetrics and gynecology subspecialist fetomaternal or MFM physicians.

We assessed placental weight and centrifuged samples for ELISA (Lifespan Biosciences, Inc.) analysis of CyP-A, NF-κB, PARP-1, and apoptosis index (TUNEL). We collected blood and placenta samples for analysis. The blood sample was taken from the antecubital vein for hemoglobin, leukocyte, platelet, hematocrit, prothrombin time, and activated partial thromboplastin clotting time compared to control, random blood glucose and glycated hemoglobin.

We chopped placenta tissue and analyzed its homogenate representing extracellular and intracellular biomolecules with different mechanisms. The placental was placed into the phosphate-buffered saline (PBS) pot and stored at -70°C before homogenization and was ready for two times 5,000 rpm centrifugation (Precellys 24), followed by intermittent incubation for 10 minutes three times each. The remaining placenta was stored on a closed pot filled with 70% formalin for IHC analysis.

We blocked-cut the full thickness of the placenta into 1 cm sizes and stored at 4°C before immunohistochemistry examination using the indirect method of Labeled-Streptavidin Biotin (LSAB). We detected the DENV-3 proteins using the commercial HR Starr Trek Universal Detection System (Biocare Medical®) kit. We identified NF-κB, PARP-1, and Cyp A by applying anti-NF-κB (ab16502) with a concentration of 1:500, anti-PARP-1 with a concentration of 1:10 (HPA045168), and anti-Cyclophilin A (ab41684, Abcam commercial anti-CyPA antibody) with a concentration of 1:100. We labeled the secondary antibodies with biotin/biotinylated secondary antibodies, namely Trekkie Universal Link (Biocare Medical®). We indicated positive results (+) in 5 visual fields by the existence of the dark brown intracytoplasmic material, and negative (-) results by its absence using Nikon Eclipse 80i displayed at 400x magnification. We referred to the expression level using strong for two positive (++) up to three positive (+++) versus weak or no staining for zero positive (0) up to one positive (+) based on.

For TUNEL analyses, we cut placental tissue followed by deparaffinization, rehydration, and pretreatment before TUNEL solution incubation with the last consecutive procedure were counterstaining, dehydration, and clearing. We used In Situ Cell Death

Detection Kit, POD (Roche, Germany) and followed the manufacturer's guideline. For each TUNEL assay, 10 visual fields were photographed at 400x magnification, and a total of 300-600 syncytiotrophoblast cells were counted in each group. Apoptotic cells were easily distinguished by occult colors, whereas normal cells were green. The total nucleus of syncytiotrophoblast cells (apoptotic cells + normal cells) and apoptotic cells were calculated. The apoptotic index was calculated by the formula (total apoptotic cells/apoptotic cells + normal cells) * 100.

We used a t-test or Mann-Whitney tests to analyze differences in blood tests, cardiovascular function, and biomolecules. We used SPSS version 26 for analyzing the data. Prior to applying these tests, data distribution was assessed using the Shapiro-Wilk test. Variables with normal distribution (Maternal Age, Maternal BMI, Body Surface Area, Hemoglobin Level, Hematocrit Level, Platelet Level, Birth Weight, Placental Weight, Diastolic Pressure, Cardiac Output, Cardiac Index, CyP-A, NF-κB, and TUNEL) were analyzed using independent t-tests, while non-normally distributed variables (Gestational Age, Leukocyte Level, Prothrombin Time, Activated Plasma Thrombin Time, Random Blood Sugar, Systolic Pressure, Total Peripheral Resistance, and PARP-1) were evaluated using Mann-Whitney U tests.

Result

This study analyzes PE through maternal and fetal characteristics (Table 1), cardiovascular function indices (Table 2), and focusing to evaluate the expression of biomolecules (CyP-A, NF-κB, PARP-1) and apoptotic index through TUNEL Assay. Details of the biomolecules comparisons, presented in Table 3 and Figure 1, revealed that while CyP-A, NF-κB, and PARP-1 did not demonstrate statistically significant differences between the NS-PE and NP groups. CyP-A levels were higher in the NS-PE group (1,629.00 ± 589.57) compared to the NP group (1,341.46 ± 674.79, p = 0.241).

NF-κB expression were slightly elevated in the NS-PE group (49.99 ± 21.47) compared to the NP group (49.30 ± 27.63, p = 0.942). PARP-1 expression also showed an increase in the NS-PE group (13.16; 3.10–32.78) compared to the NP group (11.03; 3.95–40.53, p = 0.613). (Figure 1 and Table 3). The TUNEL assay results revealed a significantly higher (p = 0.044) between the NS-PE (41.56 ± 24.87) and the NP groups (23.96 ± 18.79) (Figure 1 and Table 3).

Discussion

Cyclophilin A (CyP-A) acts as a pro-inflammatory factor, while NF-κB and PARP-1 are involved in inflammation and cellular stress, suggesting a role in the complex pathogenesis of PE. Cyclophilin A secretion occurs in response to inflammatory stimuli and vascular dysfunction, particularly affecting trophoblasts and endothelial cell function.[13, 14] Once releases, CyP-A binds to CD147, activating key intracellular signaling pathways such as extracellular signal-regulated kinase (ERK) and Phosphatidylinositol-3-kinase/Protein Kinase B (PI3K/Akt), which subsequently trigger NF-κB activation.[14] This leads to the nuclear translocation of NF-κB and promotes the production of pro-inflammatory cytokines, including Interleukin-6 (IL-6), Tumor Necrosis Factor- α (TNF-α), and Interleukin-1β (IL-1β). These cytokines further exacerbate endothelial dysfunction and contribute to the development of hypertension,[13, 15] ultimately resulting in poor placental perfusion—a hallmark of PE.[13]

In the present study, CyP-A expression was notably higher in the NS-PE compared to the NP group, as previously found,[13, 14] confirming earlier study that suggest Cyp-A upregulation was found in the

Table 1 Maternal and Fetal Characteristics in NS-PE and NP

Variable	NS-PE N: 14	NP N: 14	*p* -value
	Mean (±SD) or Median (min-max)		
Maternal Age (year)	29.00 (±7.24)	32.07 (±5.21)	0.209[a]
Gestational Age (week)	38.00 (30-40)	38.00 (37-40)	**0.020[b]**
Maternal BMI (kg/m^2)	33.67 (±5.14)	27.75 (±4.63)	**0.004[a]**
Body surface area (m^2)	1.75 (±0.02)	1.73 (±0.09)	0.612[a]
Hemoglobin level (g/dL)	12.07 (±1.10)	12.25 (±1.12)	0.674[a]
Hematocrit level (%)	35.28 (±3.81)	34.50 (±2.59)	0.533[a]
Leukocyte level ($x10^9/L$)	10,000.00 (8,000-16,400)	8,400.00 (5,700-15,800)	**0.013[b]**
Platelet level (mcL)	296,928.57 (±66,433.85)	251,285.71 (±52,216.16)	0.054[a]
Prothrombin time	10.40 (3.00-14.04)	10.10 (2.00-24.04)	0.581[b]
Activated plasma thrombin time	28.05 (10.00-34.04)	25.55 (10.00-29.00)	0.077[b]
Random blood sugar (mg/dL)	89.50 (64.00-164.00)	95.00 (80.00-119.00)	0.765[b]
Birth weight (gram)	2,786.86 (±631.07)	3,120.57 (±264.12)	0.085[a]
Placental weight (gram)	531.36 (±114.40)	604.21 (±93.07)	0.076[a]

Note: NS-PE: Non-Severe Preeclampsia; NP: Normal Pregnancy; [a]T-test Analysis; [b]Mann Whitney; SD = standard of the deviation; p =probability; the bold values represented statistically significant p-values

Table 2 Cardiovascular Function Indices in NS-PE and NP

Variable	NS-PE n: 14	NP n: 14	*p*-value
	Mean (±SD) or Median (min-max)		
Systolic	155.00 (150-205)	115.00 (100-147)	**<0.000[b]**
Diastolic	108.79 (±13.99)	72.79 (±6.57)	**<0.000[a]**
Heart rate (x/minute)	82.00 (80.00-108.00)	80.00 (72.00-106.00)	0.192[b]
Cardiac Output (L/min)	6.24 (±2.33)	5.34 (±1.39)	0.224[a]
Cardiac Index ($L/min/m^2$)	3.72 (±0.92)	3.22 (±0.69)	0.117[a]
Total peripheral resistance (MAP*80/CO)	1,590.79 (902.34 – 6303.03)	1,346.99 (980.39 – 3207.37)	0.118[b]

Note: NS-PE: Non-Severe Preeclampsia; NP: Normal Pregnancy; [a]T-test Analysis; [b]Mann Whitney; SD = standard of the deviation; p =probability; the bold values represented statistically significant p-values

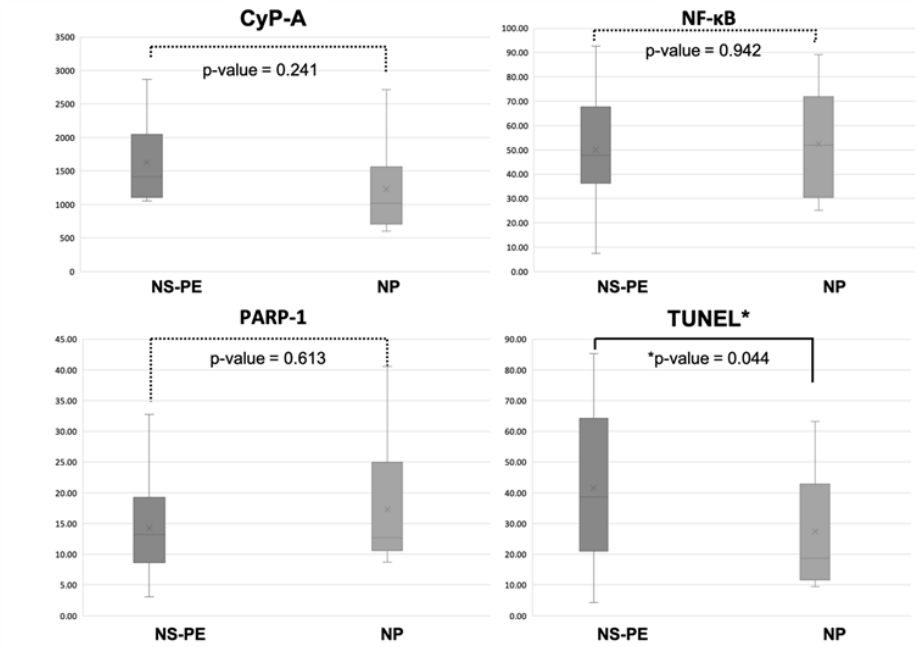
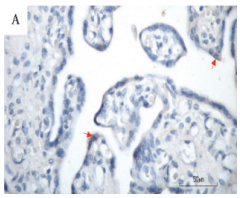
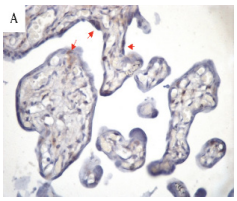
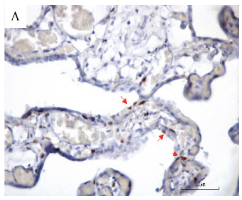
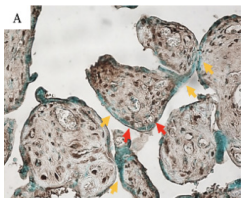
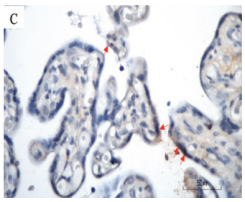
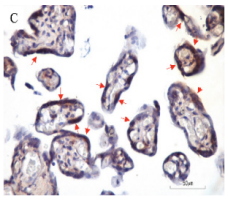
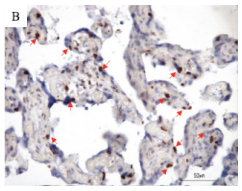
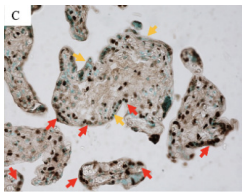


Figure 1. Bar chart of Cyclophilin A, NFKB, PARP-1, and TUNEL (apoptotic index)

Note: NS-PE: Non-Severe Preeclampsia; NP: Normal Pregnancy; the bold lines represented statistically significant p-values; dotted lines showed unsignificant statistically p-values.

Table 3 Immunohistochemistry Result in NS-PE and NP

	CyP-A Expression	NF-Kβ expression	PARP-1 expression	TUNEL expression
NP				
NS- PE				
	Higher Cyclophilin A expression in NS-PE compared to NP showing a severe syncytiotrophoblast damage in mitochondria, endoplasmic reticulum, nucleus and basal membrane.	Higher NF-Kβ expression in NS-PE compared to NP due to prolonged and severe inflammation insyncytiotrophoblast.	Higher in PARP-1 expression in NS-PE compared to NP, indicating its binding ability limited to the nucleus.	Higher apoptotic index in NS-PE compared to NP. Apoptotic cells (brown). Normal cells (green). Indicating severe syncytiotrophoblast damage due to severe and prolonged inflammation
	Syncytiothropoblast villous was stained with immunohistochemical, original magnification 400x, using Nikon Eclipse 80i, analyzing and counting with image J software, for NF-Kβ, PARP-1, Cyclophilin A while for apoptotic index (TUNEL), analyzing with ZEN software, photo using software NIS-Element Basic Research 3.2			

Note: This table shows immunohistochemistry assay result of biomolecules (CyP-A, NF-Kβ, PARP-1 score), apoptotic index (TUNEL) in NS-PE and NP.

cytotrophoblasts, syncytiotrophoblasts and vascular endothelial cells which associated with inflammatory stress in PE.[15] Although our subjects exhibited a milder inflammatory profile, the elevated CyP-A levels in NS-PE support its early involvement in the PE inflammatory cascade.

The activation of NF-κB in preeclampsia (PE) plays a central role in promoting pro-inflammatory pathways, as its elevated expression is linked to increased cytokine production and endothelial dysfunction.[16] NF-κB regulates key processes such as inflammation and oxidative stress.[17] While it is physiologically active during early pregnancy—especially in embryo implantation—its excessive activation in PE leads to immune imbalance and vascular injury.[18] Tumor Necrosis Factor (TNF) activates NF-κB, initiating a pro-inflammatory cascade relevant in PE.[18] Studies have shown NF-κB hyperactivation in PE, including elevated serum levels.[19] This state enhances pro-inflammatory cytokines, suppresses anti-inflammatory responses, and increases oxidative stress and leukocyte infiltration in the endothelium, contributing to vascular dysfunction.[17]

As inflammation progresses, PARP-1 activation occurs in response to oxidative stress and DNA damage. As coactivator of NF-κB, PARP-1 regulates proinflammatory target genes expression by entailing acetylation of PARP-1 via p300/CBP for PARP-1 and NF-κB interaction as a form of reaction of inflammatory stimulus induced apoptosis.[9, 20] PARP-1 normally facilitates DNA repair, but its excessive activation leads to placental cell death.[14] The pleiotropic roles of NF-κB and PARP-1 in PE are evident in their multifaceted involvement in inflammation, oxidative stress, and placental dysfunction.[21, 22] Despite its functional role, our data did not show significant differences in PARP-1 expression between groups, possibly reflecting individual variation in inflammatory adaptation amplify its pleiotropic characteristic.[23] Thus, investigating through inflammatory cytokine related to NF-κB and PARP-1 cascade pathway, such as IL-6, TNF-α, and IL-1β, in the future research might give better view for the complete understanding.

The TUNEL assay confirmed a significantly elevated apoptotic index in NS-PE placentas.[24] These findings are in line with studies such as Sharma et al., which demonstrated increased apoptosis and impaired trophoblast invasion in PE placentas,[11] who evaluated the apoptotic index across all placental regions, revealing failed placental invasion and necrosed syncytial knots, as confirmed by the IHC assay (Figure 2).

Overall, the dysregulated CyP-A–NF-κB–PARP-1 signaling pathway leads to preeclampsia progression, manifesting as hypertension, fetal distress, and adverse pregnancy outcomes.[25] This cascade highlights the significant role of CyP-A in initiating inflammation, amplified by NF-κB, and PARP-1 in sustaining cellular damage.

This study highlights the potential of molecular profiling for early detection of preeclampsia (PE), focusing on the expression of CyP-A, NF-κB, and PARP-1. Although limited by a small sample size and the absence of pre-pregnancy BMI data, all subjects met inclusion criteria without maternal or fetal complications. Immunohistochemistry of placental tissues post-delivery revealed inflammatory patterns associated with NS-PE, though the analysis was limited to terminal pregnancy samples. The study did not assess key cytokines such as IL-6, TNF-α, and IL-1β, which may be critical to understanding the CyP-A, NF-κB, and PARP-1 signaling cascade. Additionally, the TUNEL assay alone may not fully capture apoptotic dynamics.

In conclusion, increased expression of CyP-A, NF-κB, and PARP-1 suggests a significant role for inflammation in vascular endothelial injury and the early stages of hypertension in NS-PE. Elevated apoptosis, as shown by the TUNEL assay, may further contribute to maternal and fetal risks, warranting comprehensive investigation. To advance our understanding, future research should involve larger cohorts, evaluate a broader spectrum of complications, and incorporate both intracellular and extracellular markers—including pro-inflammatory cytokines—to better elucidate the underlying mechanisms.

Conflict of Interest

There is no conflict of interest.

Advice and Thanks

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