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The Hidden Face of Obesity: The Role of Inflammation

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ABSTRACT

Aim: This study explores the interaction between elevated proinflammatory cytokines, part of the body's inflammatory response, and obesity, also known as low-grade inflammation. The aim is to clarify whether the increased levels of adipocytokines contribute to the development of obesity or if obesity itself enhances the production of adipocytokines. Understanding the reciprocal relationship between these two factors could facilitate the development of new strategies for preventing and treating obesity-related complications. **Results**: In people with obesity, changes occur in various metabolic pathways as the body's energy balance shifts, with inflammation being the primary driver of these alterations. Inflammation influences key adipokines such as adiponectin and leptin and interacts with other biological processes. The literature suggests that a diet rich in complex carbohydrates, high fiber, and low glycemic index foods is linked to reduced proinflammatory cytokines. The Mediterranean and anti-inflammatory diets are clinically recommended for managing inflammation. However, determining the root cause of inflammation requires a detailed exploration of several interconnected mechanisms. **Conclusion:** Determining the root cause of inflammation requires thorough examination. The ongoing debate is whether increased cytokine inflammatory responses trigger obesity, or whether obesity itself initiates inflammation by amplifying cytokine responses. Further research is needed to clarify the long-term implications of this complex relationship.

Keywords: Adipocytokines, Cytokines, Inflammation, Nutrition, Obesity

Obezitenin Gizli Yüzü: İnflamasyonun Rolü

ÖZ

Amaç: Bu çalışma, vücudun inflamatuar tepkisinin bir parçası olan yüksek proinflamatuar sitokinler ile düşük dereceli inflamasyon olarak da bilinen obezite arasındaki etkileşimi araştırmaktadır. Amaç, artan adipositokin seviyelerinin obezitenin gelişimine katkıda bulunup bulunmadığını veya obezitenin kendisinin adipositokinlerin üretimini artırıp artırmadığını açıklığa kavuşturmaktır. Bu iki faktör arasındaki karşılıklı ilişkinin anlaşılması, obeziteye bağlı komplikasyonların önlenmesi ve tedavisi için yeni stratejilerin geliştirilmesini kolaylaştırabilir. **Bulgular:** Obezitesi olan kişilerde, vücudun enerji dengesi değiştikçe çeşitli metabolik yollarda değişiklikler meydana gelir ve bu değişikliklerin birincil itici gücü inflamasyondur. İnflamasyon, adiponektin ve leptin gibi temel adipokinleri etkiler ve diğer biyolojik süreçlerle etkileşime girer. Literatür, kompleks karbonhidratlar, yüksek lif ve düşük glisemik indeksli gıdalar açısından zengin bir diyetin proinflamatuar sitokinlerin azalmasıyla bağlantılı olduğunu göstermektedir. Akdeniz diyeti ve anti-inflamatuar diyetler, inflamasyonu yönetmek için klinik olarak önerilmektedir. Bununla birlikte, inflamasyonun temel nedenini belirlemek, birbirine bağlı çeşitli mekanizmaların ayrıntılı bir şekilde araştırılmasını gerektirir. **Sonuç:** İnflamasyonun temel nedenini belirlemek kapsamlı bir inceleme gerektirir. Devam eden tartışma, artan sitokin inflamatuar yanıtlarının mı obeziteyi tetiklediği, yoksa obezitenin kendisinin mi sitokin yanıtlarını güçlendirerek inflamasyonu başlattığıdır. Bu konuyu açıklığa kavuşturmak için daha fazla araştırmaya ihtiyaç vardır.

Anahtar Kelimeler: Adipositokinler, Beslenme, Sitokinler, İnflamasyon, Obezite

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INTRODUCTION

Obesity is fat accumulation in the body that may pose a health concern (Masood & Moorthy, 2023). People with Body Mass Index (BMI)> 30 kg/m2 are classified as obese (Masood & Moorthy, 2023; Murray et al., 2020). In the Lancet report, the number of people with obesity over the age of 18 in 2022 is stated to be more than 890 million (Murray et al., 2020). Obesity represents a significant public health concern, manifesting across all age demographics (Phelps et al., 2024). To exemplify, in 2022, it is estimated that 37 million children under 5 may be obese (Sing & Srivastava, 2024). In Africa, this rate has been 23% higher since 2000 (Okunogbe et al., 2022). In the adolescent population, this number is estimated to be 390 million or more between the ages of 5-19 (Murray et al., 2020). In this age group, obesity increased by 12% between 1990 and 2022 (Murray et al., 2020). High BMI levels are not only a danger factor for obesity. Still, it may also lead to some metabolic diseases such as type 2 diabetes (T2DM), insulin resistance (IR), cardiovascular diseases (CVD), or various types of cancer. Although the causes of these diseases are often unclear, comorbidities are intertwined and associated with low levels of chronic inflammation. In general, three stages are typically associated with chronic inflammation: (a) an acute, adaptive inflammatory response, (b) a protracted maladaptive phase that results in consequences, (c) an initial trigger, which is typically some type of stressor (Reilly & Saltiel, 2017). To explain, initial stress in chronic inflammatory disorders triggers a physiological adaptive response aimed at mitigating the stress (Hotamisligil, 2006). This initiated adaptive reaction eventually transforms into a pathologically harmful response. The first step toward obesity is homeostatic stress, which is brought on by anabolic pressure brought on by positive energy balance (Hall & Guo, 2017). The catabolic adaptive inflammatory response lowers the anabolic pressure and encourages the growth of fat tissue. Long-term obesity has pathological implications because the body attempts to find a new balancing point for blood glucose and weight throughout time (Phelps et al., 2024). This article aims to discuss prospective therapeutic options for obesity-induced inflammation and to assess the likelihood of cellular and molecular triggers of obesity-induced inflammation.

Cytokines

Cytokines, also known as polypeptides, are released and synthesized by various cell types, controlling inflammatory and immunological processes such as inflammation, cell division, wound healing, and the overall body's response to damage (Balkwill, 2001). They start to be produced and secreted when immunological stimulation occurs (Karin & Clevers, 2016). Through the use of tyrosine kinases, cytokines attach to membrane receptors and initiate gene expression (Akdoğan & Yöntem, 2018). Membrane proteins change their amount in response to cytokines. Cytokines are characterized in four ways: pleiotropic, redundant, agonist, and antagonist. Pleiotropic cytokines have activity in different and diverse cells, while redundant cytokines are different cytokines but have similar effects (Akdoğan & Yöntem, 2018). Depending on their source or function, cytokines are divided into several groups that are pro-inflammatory cytokines, chemokines, immunomodulatory cytokines, antiviral cytokines, and anti-inflammatory cytokines (Dinarello, 2000; see Table 1).

Table 1. Classification of cytokines

Proinflammatory cytokines	Chemokines	Anti-inflammatory cytokines	Immunomodulatory cytokines	Antiviral cytokines
Tumor necrosis factor-alpha (TNF-α)	Monocyte chemoattractant protein 1 (MCP-1)	Interleukin-10 (IL-10)	Interleukin-2 (IL-2)	Interferon alpha (IFN-α)
Interleukin-1 (IL-1)	Interkeukin-8 (IL-8)	Transforming growth factor beta (TGF-β)	Interleukin-4 (IL-4)	Interferon beta (IFN-β)
Interleukin-6 (IL-6)			Interleukin-12 (IL-12)	
Interferon gamma (IFN- γ)				

Activated macrophages release TNF-α in reaction to microorganisms, particularly Gram-negative bacteria that release lipopolysaccharide (LPS) (Akdoğan & Yöntem, 2018). It is a crucial acute inflammatory mediator. Activated macrophages also create the inflammatory cytokine IL-1 (Dinarello, 2000). It has effects very similar to those of TNF-α. Type-1 Helper (Th1) cells are the primary producers of significant IFN-γ, which boosts the cellular immune system and aids in the destruction of diseased cells (Wu & Ballantyne, 2020). IL-10, a cytokine that belongs to the anti-inflammatory cytokines class, is defined as a factor that inhibits cytokine synthesis and is produced by Type-2 Helper (Th2) cells, which are involved in humoral immunity and B antibody production (Akdoğan & Yöntem, 2018; Demirci et al., n.d.; Wu & Ballantyne, 2020). T lymphocytes and other types of cells create TGF-β. Mostly, TGF-β is an inhibitory cytokine. It prevents T-cell growth and the activation of macrophages (Li & Flavell, 2008). By interacting with endothelial cells, TGF-β may also prevent the effects of pro-inflammatory cytokines (Yoshimura et al., 2010). Chemotactic cytokines, or chemokines, are released by several leukocyte and other cell types (Murphy & Weaver, 2017). They are molecules that guide leukocytes to infection sites and play a part in deciding which cells need to cross the

epithelium and where the leukocytes go (Akdoğan & Yöntem, 2018). T-helper cells produce IL-2. It is the primary T-cell growth factor. IL-2 stimulates B cells and activates monocytes and Natural Killer (NK) cells, which are big granular lymphocytes and the most significant innate immune cells (Letafati et al., 2024). When it comes to T-cells, IL-2 has an autocrine effect, meaning it works well for self-signaling (Akdoğan & Yöntem, 2018; Wu & Ballantyne, 2020). IL-12 is produced by activated macrophages and dendritic cells. It promotes T-helper cell development into Th1 cells and increases IFN-γ production (Bream et al., 2003; Hamza et al., 2010). Furthermore, IL-12 improves NK cells' capacity for cytolysis (Bream et al., 2003).

Inflammation Types

Two categories of inflammation are Type 1 and Type 2. The factor that differentiates these two types is related to the responses of the immune system. It is regulated by the t-helper and is related to different cytokines. Type 1 inflammation is regulated by Th1 cells, while type 2 inflammation is regulated by Th2 cells (Navab et al., 2008). Pro-inflammation is often referred to as type 1 inflammation, while anti-inflammation is also referred to as type 2 inflammation (Navab et al., 2008; Unamuno et al., 2018). Table 2 illustrates the distinction between type 1 and type 2 inflammation.

Table 2. Type 1 vs 2 Inflammation Comparison

Functions	Type 1	Type 2
Controlled by	Th1	Th2
Cytokines secreted by	TNF-α, IL-6, IFN-γ, IL-12	IL-4, IL-5, IL-10 TGF-β
Immune response	Cellular Immunity	Humoral Immunity
Target pathogens	Intracellular pathogens	Extracellular pathogens

TGF-β; transforming growth factor-beta, TNF-α; tumor necrosis factor alpha, IL; interleukin, INF; Interferon, Th; T-helper.

Adipose Tissue and Adipocytokine

The cells in the body that store fat are called adipocytes, or fat cells. They perform a variety of roles in metabolism, hormone secretion, and energy storage (Rosen & Spiegelman, 2006). The tissue in the body that stores fat is referred to as adipose tissue. Adipocytes, the building blocks of adipose tissue, perform many bodily tasks including hormone synthesis, energy storage, and metabolic control (Trayhurn & Wood, 2004). In conclusion, adipose refers to the tissue composed of fat cells, while adipocytes are individual fat cells. Among these phases are those of adipocyte hyperplasia, which is characterized by an increase in cell number, hypertrophy-induced adipose tissue expansion, immune cell infiltration, and extracellular matrix modification (Ferrante, 2013; Galic et al., 2010; Wang et al., 2013). The equilibrium of adipocytokines generated in adipose tissue is crucial for maintaining the homeostasis of lipid and glucose metabolism. In obese people, the adipose tissue adapts to an excess of calories by going through several cellular and structural processes (Yoshimura et al., 2010). Even while obesity is a danger factor in and of itself, an untreated, persistently growing inflammation throws these phases out of balance. As a result, there is an increase in adipogenesis, lipid storage, pro-inflammatory adipokines, and regional hypoxia, which is characterized by altered adipose tissue lipid composition and reduced adipose tissue function (Unamuno et al., 2018; Wang et al., 2013). Based on the lipid droplets found within its cells, adipose tissue is categorized as unilocular, known as white adipose tissue (WAT), or multilocular, known as brown adipose tissue (BAT) (Unamuno et al., 2018; Wang et al., 2013). WAT is composed of two types of adipose tissue: visceral (VAT) and subcutaneous (SAT). VAT is characterized as tissue that extends around the intra-abdominal organs and is deeper than subcutaneous adipose tissue in the lower abdomen and back of the waist, raising the risk of metabolic disease (Pellegrinelli et al., 2016). BAT enhances thermogenesis because it has mitochondria with a greater capacity to metabolize fatty acids and glucose, as well as tiny lipid droplets. To manage obesity, BAT activation is therefore considered a therapeutic approach (Gaspar et al., 2021).

Adipokines or adipocytokines are cytokines secreted by adipose tissue. Adipocytokines are also known as adipose-tissue-derived hormones. Adipocytokines are crucial for maintaining the equilibrium of fat and glucose metabolism (Polson & Thompson, 2004). These characteristics make adipocytokines promising target molecules for the management of obesity and its associated comorbidities, which are crucial for preserving energy balance (Valsamakis et al., 2004). There are several categories into which adipocytokines are divided. They fall into two categories based on physiological classification that are insulin resistance-inducing factors and insulin-sensitive factors (Wang et al., 2013). In addition to this, they are classified as i) hormones produced simultaneously with adipose tissue production in other tissues or organs, ii) the main source is white adipose tissue and other cells in adipose tissue iii) hormones produced only by adipocytes in white adipose tissue (Galic et al., 2010; Pellegrinelli et al., 2016). Adipocytokines secreted from adipose tissue are mainly the following: leptin, TNF-α, adiponectin, resistin, renin-angiotensin system (RAS) proteins, IL-6, retinol binding protein-4 (RBP4) (Ouchi et al., 2011).

Adiponectin

Adipocytes in adipose tissue release and generate adiponectin, which has pleiotropic effects in various tissues such as the liver, pancreatic β-cells, immunological cells, and is especially implicated in the mechanism of appetite and energy in the body (Ouchi et al., 2011). It has been discovered that adiponectin is released from adipose tissue as well as from human and mouse skeletal muscle, as well as from cardiomyocytes (Brochu-Gaudreau et al., 2010). Depending on the receptor it binds to, adiponectin has several signaling pathways. Findings by Yamauchi et

al. indicate that AdipoR 1 and AdipoR 2 receptors activate AMP (adenosine monophosphate) activated protein kinase (AMPK) and Peroxisome proliferator-activated receptor alpha (PPAR-α), respectively (Yamauchi et al., 2004). These receptors' functional organs also differ. Skeletal muscle normally expresses AdipoR 1, while the liver typically expresses AdipoR 2 (Yamauchi et al., 2004). Adiponectin has three primary actions: it stimulates insulin, inhibits apoptosis, and reduces inflammation. Despite the fact that adiponectin primarily acts on fat, the heart, kidney, liver, and pancreas, it may also reach other tissues due to the large number of adiponectin receptors (Velojic-Golubovic et al., 2013). Research has indicated a negative correlation between body mass index and body plasma levels of adiponectin (Brochu-Gaudreau et al., 2010). Once more, leptin and adiponectin alterations released from adipose tissue have been linked to disorders like reduced insulin sensitivity and glycemic irregularity in obesity, which is characterized by an increase in fat in the central region with body weight (Ouchi et al., 2011). Furthermore, adiponectin has a more significant role in the restoration of insulin sensitivity following weight loss (Xydakis et al., 2004).

Leptin

Polypeptide leptin is released by the liver, placenta, and adipose tissue. The main functions include inhibiting food intake and contributing to energy homeostasis (Blüher & Mantzoros, 2015). Additionally, it is said to restrict the amount of lipids that may be stored in the tissue that secretes it. When fatty acid production is reduced and oxidation is initiated, adipocytes produce glycerols. The development of triglyceride-synthesizing genes is inhibited by this mechanism (Blüher & Mantzoros, 2015). In the regulation of hormones, these are hormones like LH and TSH, which may be regulated by leptin (Oswal & Yeo, 2010). Leptin signaling is carried out by the hypothalamic arcuate nucleus (ARC). Proopiomelanocortin (PMC) and Neuropeptide Y (NPY) are important neuron classes for Agouti-related protein (AgRP) signaling. PMC reduces food intake, while NPY and AgRP promote food intake (Oswal & Yeo, 2010). Leptin receptors are highly expressed in all of these neurons (Coll et al., 2008). It is well known that leptin receptors and cytokine receptors have structural similarities (Tartaglia, 1997). The central nervous system (CNS) uses the ObRa and ObRc leptin receptors, which are found in blood-brain barrier capillaries, to transport leptin . Rats with impaired ObR receptor function and rats given obesity-induced leptin transport abnormalities were studied (Gray & Vidal-Puig, 2008). This impairment was linked in this investigation to an overabundance of endogenous leptin. Similar to these results, another research discovered that serum leptin perfusion corrected the course of leptin in rats lacking the ObR receptor (Banks et al., 2002). Given this knowledge, leptin resistance indicates that obesity has hampered the leptin's mode of action. Obesity-related increases in lipid concentrations in adipocytes as well as their size, are variables that have a direct impact on the Ob-gene program (Banks et al., 2002). In the process of inflammation, leptin appears as leptin resistance. Changes in energy homeostasis and leptin resistance are caused by inflammation, which is mediated by ARC. Obesity is thought to result from changes in a person's dietary intake. Interactions are initiated by the CNS and adipocytes (Pérez-Pérez et al., 2020). Adipose tissue malfunction and elevated production of proinflammatory cytokines and adipokines are the results of the interactions. This interplay also impacts the degree of persistent inflammation in the brain. Due to the inhibition of leptin receptors by the Janus Kinases (JAK)/Signal Transducer and Activator of Transcription (STAT) pathway, leptin resistance may develop (Pérez-Pérez et al., 2020). Protein tyrosine phosphatases-1B (PTP1B) start the process of inhibition.

Nutrition in Inflammation

It is indisputable that the human diet directly affects the immune system. This kind of nourishment needs to be balanced, though. To conceptualize this balanced connection as two distinct categories—overnutrition and undernutrition—an individual who is overfed has excessive immune activation of inflammatory pathways, whereas an individual who is undernourished experiences immunosuppression (Figure 1, 2). Carbohydrates and fats, probiotics, prebiotics, vitamins, and minerals play a significant role in the relationship between inflammation and nutrition.

Carbohydrates

One of the most crucial dietary components—carbohydrates—has a significant impact on obesity risk. The glycemic load of the diet and the glycemic index of the foods consumed must be taken into account to provide appropriate nutrition. The term “glycemic index (GI)” refers to a metric that quantifies how much dietary carbohydrate intake affects blood glucose, or blood sugar levels. The overall amount of sugar in blood sugar brought on by the carbohydrate content of the meals eaten at any one meal is known as the “glycemic load (GL)”(Augustin et al., 2015). Research has demonstrated a substantial association between the glycemic load ratio and growing levels of cytokines and the glycemic index divided by the latter (Levitan et al., 2008). Low plasma adiponectin levels were linked to increased glycemic load and index in another investigation of healthcare workers (Johnson & Makowski, 2015). Another research, in contrast to predictions, did not demonstrate a significant correlation between high glycemic index and load and cytokines like TNF-α (Pittas et al., 2006). Furthermore, one study shows that a dietary pattern high in refined carbohydrates during adolescence is associated with higher concentrations of IL-6 in the body later in life (Goletzke et al., 2014). The study showed that adherence to a low-carbohydrate dietary pattern increased TGF-β and interleukin-1β (IL-1β) levels in obese women, which positively affected circadian rhythm (Tavakoli et al., 2021).

Fats

It is clear that saturated fatty acids activate signaling in inflammatory cascades (Zhou et al., 2020). Palmitate has been demonstrated to stimulate the NF-κB pathway,

thereby increasing the expression of pro-inflammatory cytokines such as TNF-α and IL-6 in adipocytes and macrophages (Zhou et al., 2020). This activation is associated with TLR4 signaling, which contributes to a persistent inflammatory state in adipose tissue that is characteristic of obesity (Luca and Olefsky, 2007). Furthermore, studies have demonstrated that short-chain fatty acids may sensitize dendritic cells, thereby triggering inflammation in people with obesity due to increased Th1 and Th17 responses (Stelzner et al., 2016). Diets high in fat, particularly those high in trans fats, lead to the buildup of body fat and alter immune system pathways. A high trans-fat diet was linked to an increase in the pro-inflammatory cytokine IL-6 in a 730-person cohort study (Lopez-Garcia et al., 2005). In another study, when an 8% trans fat load was added to the high-fat diet profile, CRP levels in the blood increased significantly (Baer et al., 2004). In another study of 18 men and 18 women, an increase in IL-6 levels was observed when trans fat was added to an optimal diet with 30% fat content. These individuals were diagnosed with hypercholesterolemia (Lichtenstein, 2003). Unsaturated fatty acids, such as omega-3, have anti-inflammatory properties that may counterbalance the increased inflammatory response. In a 6-week study, the group receiving 3.6 g/day of EPA/DHA showed a significant reduction in endotoxemia-induced inflammatory gene expression compared to the placebo group (Ferguson et al., 2016). Similarly, another study found that non-diabetic individuals with insulin resistance who consumed 4 g/day of EPA for 12 weeks exhibited decreased MCP-1 levels (Spencer et al., 2013).

Probiotics-Prebiotics

Probiotics and prebiotics have been shown to alleviate the chronic low-grade inflammation that is characteristic of obesity. Probiotics have been shown to regulate the body's energy expenditure and metabolism, thereby contributing to weight management. While probiotics, typically administered orally as supplements, are effective in the immune system and inflammation, the specific probiotic strains involved are also of significance (Markowiak & Śliżewska, 2017; Cani & Delzenne, 2009). In a separate study, *Propionibacterium freudenreichii ssp.* was utilized. The subjects were observed over a period of three weeks. While no alterations in IL-6 levels were observed, a decline in CRP levels was noted (Kekkonen et al., 2008). Prebiotics are non-digestible food substances that nourish and promote the growth of beneficial bacteria in the gut flora. It has been demonstrated that probiotics play a pivotal role in the mitigation of inflammation (Manzoor et al., 2022). Furthermore, the reduction of proinflammatory cytokines has been observed in response to certain vitamins and minerals (Brady et al., 1996). A study on the relationship between prebiotics and inflammation examined the effects of administering 8 grams of oligofructose supplementation to elderly individuals over 3 weeks. The study found that IL-6 levels in these individuals decreased. Conversely, in another study, malnourished individuals were administered the same supplement over 12 weeks, and no significant impact on IL-6 levels was observed (Pischon et al., 2005).

Figure 1. The relationship between overeating and inflammation

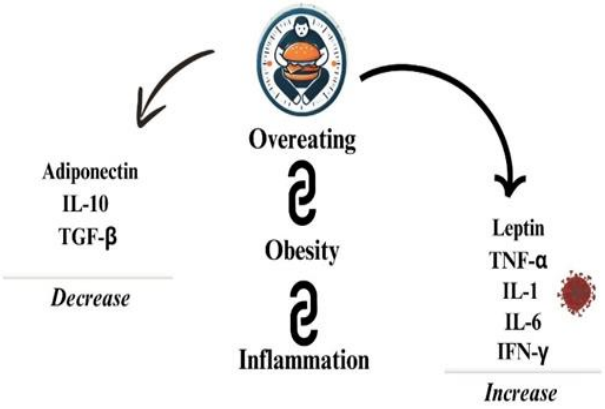
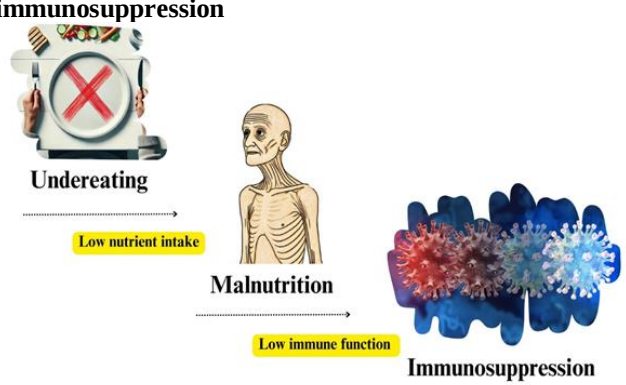


Figure 2. The relationship between undereating and immunosuppression



CONCLUSION

Numerous factors may precipitate elevated inflammatory marker levels. Given its impact on inflammatory markers, it is also understood to influence hormonal activity. Consequently, the mechanism through which obesity contributes to obesity or obesity-related inflammation is intricate. It is evident that dietary modifications, particularly those aimed at reducing systemic inflammation, have demonstrated encouraging results in the management of both inflammation and obesity. Further research is needed if full recovery is to be achieved.

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Conflict of Interest

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

Author Contributions

Plan, design: Y.A.

Material, methods, and data collection: Y.A., G.D.B.

Data analysis and comments: Y.A., G.D.B.
Writing and corrections: Y.A., G.D.B.

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