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Prasanna's Theory of Inflammatory cascade: Chronic Inflammation and Metabolic Fallout

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ABSTRACT

Type 2 diabetes mellitus has traditionally been understood through the lens of insulin resistance and pancreatic β-cell dysfunction. However, emerging evidence positions chronic low-grade inflammation as a central pathogenic driver rather than a mere consequence. Prasanna's Theory of Inflammatory Cascade proposes a unifying model wherein antecedent inflammation serves as the primary trigger for T2DM. Initiated by environmental and genetic factors—including obesity, poor diet, sedentary behaviour, and psychosocial stress—this persistent inflammatory state disrupts insulin signaling pathways and promotes β-cell exhaustion.

Once established, T2DM further propagates inflammation through mechanisms such as glucotoxicity, lipotoxicity, and oxidative stress. This bidirectional relationship creates a self-sustaining inflammatory loop, referred to as the "inflammatory cascade." Antecedent inflammation, which is the root cause of diabetes mellitus, is now further worsened by super added inflammation because of Diabetes Mellitus. As inflammation intensifies, it contributes to the pathogenesis of a spectrum of comorbid conditions, including hypertension, dyslipidemia, atherosclerosis, and non-alcoholic fatty liver disease (NAFLD), marking a progression toward full-blown metabolic syndrome.

This theory emphasizes the need for anti-inflammatory strategies—not just glucose control—as core components in the prevention and management of T2DM and its complications. Prevailing treatment strategies target the effect rather than cause. Hence the inflammatory cascade contributes to other diseases. Understanding the inflammatory underpinnings of metabolic diseases could reshape diagnostic and therapeutic approaches, supporting a more integrated, preventive model of care.

Keywords*: Type 2 Diabetes Mellitus; Chronic Low-Grade Inflammation; Inflammatory Cascade;*

INTRODUCTION

Diabetes mellitus, an epidemic of the modern era, is rarely a solitary diagnosis. It often heralds a spectrum of vascular and metabolic derangements—including hypertension, Dyslipidemia, myocardial infarction, and stroke—collectively referred to as "lifestyle diseases". Traditional diabetic management narrowly targets hyperglycemia, yet longitudinal data reveal persistently high cardiovascular morbidity and mortality, hinting at neglected underlying pathological processes.

Growing evidence supports the primacy of chronic low-grade inflammation as a unifying thread linking lifestyle diseases, with antecedents in hereditary factors, obesogenic diets, physical inactivity, substance abuse, and pollution exposure[1]. Diabetes emerges as a clinical marker of this smouldering process. Treating it in isolation neglects the expanding inflammatory milieu, thereby setting the stage for the escalation and convergence of other lifestyle comorbidities[2]. In this review, we examine current scientific understanding of antecedent inflammation's aetiology and consequences, advocating for a paradigm shift in prevention and treatment strategies.

Antecedent Inflammation: Origins and Drivers

Several factors predispose to inflammation in humans.

Genetic Predisposition

Common variants in genes encoding **TNF-α, interleukins (IL-1β, IL-6, IL-8, IL-18),** and their receptors significantly influence inflammatory disease susceptibility[3]. These genes form part of what researchers term the **"inflammatome"** - a core set of inflammation-related genes common to several chronic diseases that represents shared molecular networks underlying both inflammation and disease predisposition[4]. Mutations in the **NLRP3 gene** causes constitutive inflammasome activation. These gain-of-function mutations lead to continuous production of IL-1β and IL-18, creating a state of chronic inflammation[5].

Even common polymorphisms in NLRP3, when combined with variants in other genes like CARD8, can predispose individuals to inflammatory conditions[5]. Genetic variants in transcription factors that control inflammatory gene expression create broad effects on inflammatory susceptibility. The NF-κB pathway, which responds to multiple inflammatory stimuli, contains numerous genetic variants that alter the magnitude and duration of inflammatory responses. Similarly, variants affecting the JAK-STAT pathway influence cytokine signalling and inflammatory gene transcription[6].

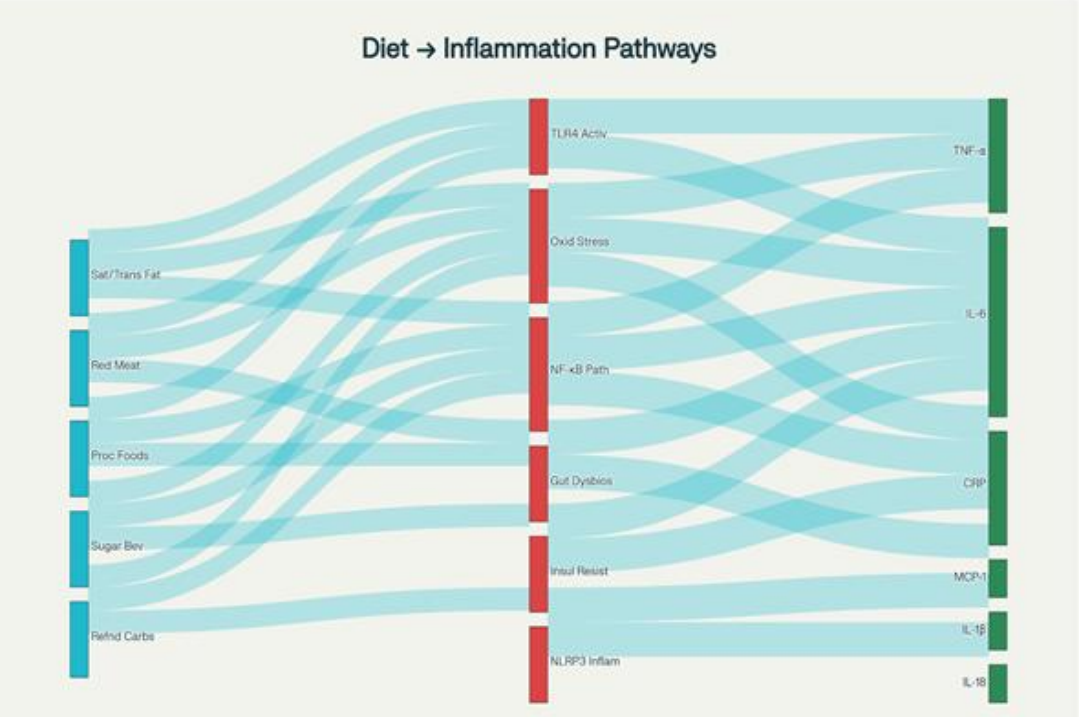
The C129S mutation in PTPN22 creates enhanced T cell signalling and more severe autoimmune inflammation in a NOX2-dependent manner. Thus, altering the redox regulation of inflammatory pathways[7]. Epigenetic changes like promoter hypomethylation of Toll-like receptor genes is associated with increased pro-inflammatory response[8].

Life style Predisposition

Dietary Factors

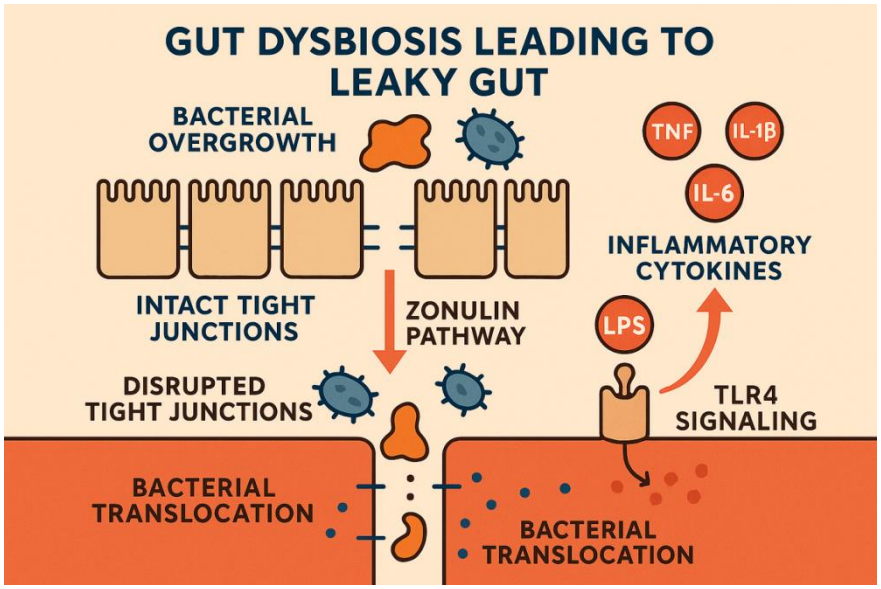
Certain foods and dietary patterns are associated with higher levels of inflammatory markers, such as C-reactive protein (CRP) and interleukins:

- **Red and Processed Meats:** High intake can elevate inflammatory cytokines[9].
- **Refined Carbohydrates:** White bread, white rice, and sugary foods rapidly digest and disrupt metabolic balance, leading to inflammation[10].
- **Added Sugars and Sweetened Beverages**: Promote immune dysfunction and increase markers of inflammation[10].
- **Saturated and Trans Fats:** Common in fried foods, processed snacks, and baked goods, these elevate CRP and interleukin levels[10].
- **High-Calorie, Processed Foods:** Diets typical of the "Western pattern" are consistently linked to higher inflammatory states and metabolic disruption[9].



Gut dysbiosis

Western diets high in refined carbohydrates, trans fats, and low fiber promote gut dysbiosis and systemic endotoxemia, activating innate immunity[11]. Imbalance in gut microbiome, leads to increased intestinal permeability ("leaky gut") and release of microbial products like LPS (Lipopolysaccharide) into circulation, further enhancing the inflammation[12].

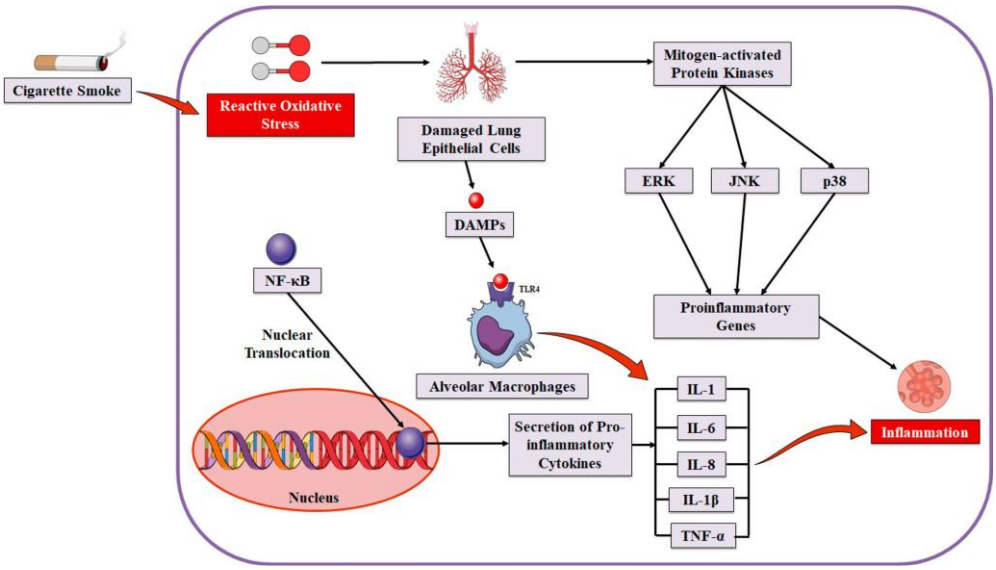


Sedentary Lifestyle

Sedentary lifestyles increase visceral fat, which is metabolically active and secretes pro-inflammatory cytokines (e.g., TNF-α, IL-6, MCP-1)[13]. Physical inactivity downregulates anti-inflammatory myokines(e.g. IL-6, IL-10, IL-1ra) and increases visceral fat, a known reservoir of inflammatory mediators[13]. Higher sedentary time correlates with elevated levels of inflammatory markers including C-reactive protein (CRP), TNF-α, and IL-6, independent of overall physical activity[14]. Visceral adipose tissue in sedentary individuals undergoes immunometabolic changes, including the loss of metabolic homeostasis and activation of damage-associated molecular patterns (DAMPs), further stimulating chronic inflammation[15].

Smoking

Cigarette smoke contains thousands of chemicals, including reactive oxygen species (ROS) and free radicals that damage cell membranes, proteins, and DNA. This damage activates cellular pathways (such as NF-κB and AP-1), leading to the production of pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-8 (IL-8)[16]. Smoking is closely associated with increased blood levels of **C-reactive protein (CRP), fibrinogen, and IL-6**—all key markers of systemic inflammation and predictors of future cardiovascular and metabolic disease risk[17].



Environmental Pollution

Exposure to particulate matter **(PM2.5, PM10)** has been shown to activate toll-like receptors and NLRP3 inflammasomes, perpetuating systemic inflammation[18]. Alveolar macrophages and bronchial epithelial cells respond to these particulate matter by producing **pro-inflammatory cytokines** (e.g., IL-6, IL-8, TNF-α), leading to local and eventually systemic inflammation[19]. Many pollutants lead to the generation of **reactive oxygen species (ROS)**, resulting in **oxidative stress** within cells. Excess ROS damage cellular proteins, lipids, and DNA, activating inflammatory signaling pathways, especially **NF-κB** and **AP-1**, which amplify cytokine and chemokine production[20].This vicious cycle between oxidative damage and inflammation both perpetuates and broadens the scope of tissue injury.

Poor sleep quality

Poor subjective sleep and shorter sleep measured by polysomnography are associated with increased inflammatory markers (CRP, IL-6, and TNF-α)[21,22].

A nexus of all the above factors triggers chronic, systemic inflammation.

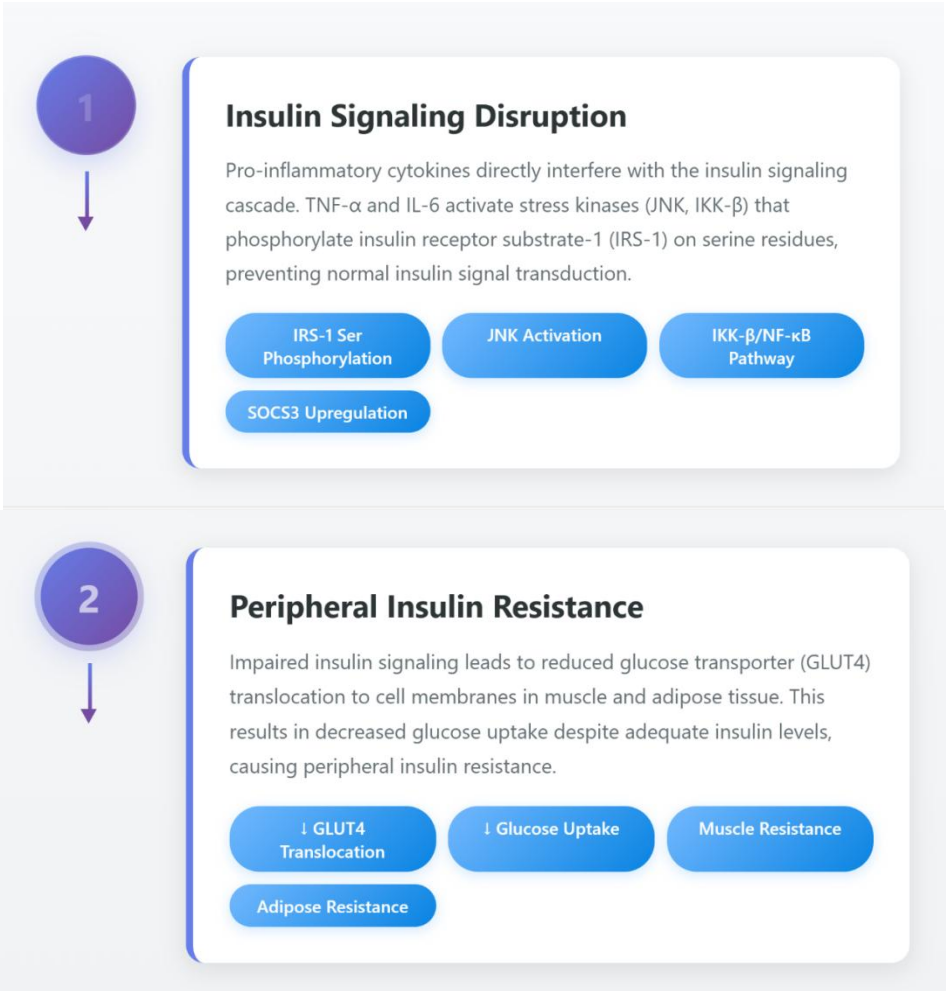
Psychological Stress and Inflammatory Pathways

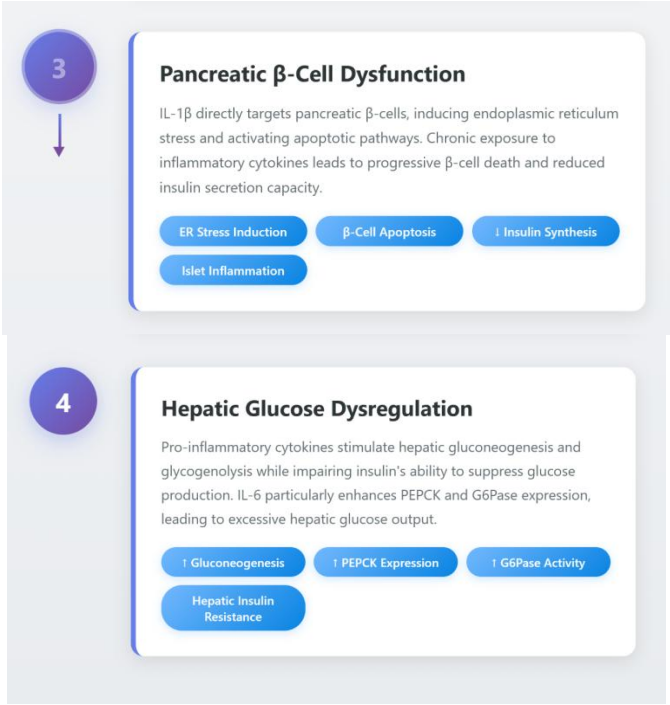
Chronic psychological stress has been shown to activate the hypothalamic-pituitary-adrenal (HPA) axis, increasing cortisol and other stress hormones. Sustained elevation of these hormones can dysregulate the immune system, leading to low-grade inflammation[22].

The Pathophysiological Impact of Chronic Inflammation on Organ Systems:

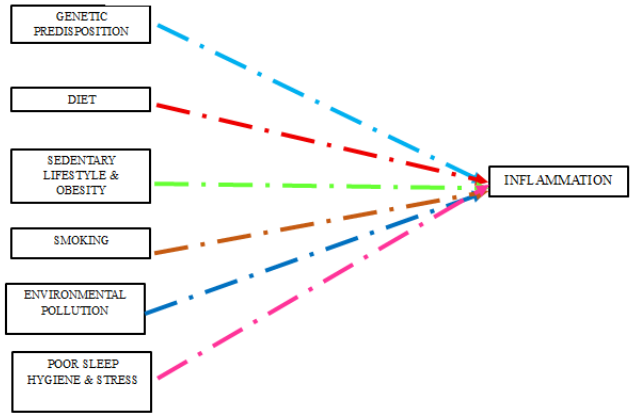
Chronic inflammation exerts a multitude of effects over various organ systems in the body. At the organ level, chronic inflammation results in vasculopathy(Endothelial Dysfunction), neuropathy and parenchymal damage through the inflammatory mediators. All the major organs of the body like Endocrine pancreas, Heart, liver, Thyroid gland.

The Islet insult and Diabetes Mellitus

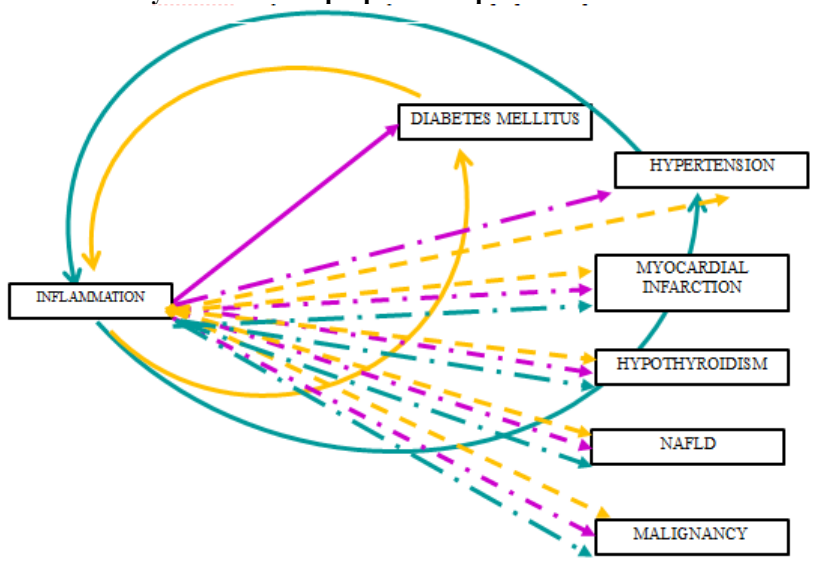




Prasanna's theory of inflammatory cascade: The perpetual loop



Prasanna's theory of inflammatory cascade: The perpetual loop



	Antecedent inflammation resulting in disease
	Subclinical inflammation driving major diseases
	Enhanced inflammation because of diabetes resulting in a self sustaining inflammatory loop
	Super added inflammation because of diabetes
	Enhanced inflammation because of hypertension resulting in a self sustaining inflammatory loop
	Super added inflammation because of hypertension

Prasanna's Theory of Inflammatory Cascade: The Perpetual Loop

Humans face constant exposure to inflammation from multiple sources. This creates a chronic proinflammatory state that affects organ systems throughout the body. The most vulnerable organ fails first, manifesting as clinical disease—but this represents only the tip of the iceberg.

This initial disease manifestation further intensifies the underlying inflammatory state. When we treat only the visible disease, the foundational inflammation continues unchecked, progressively damaging other organ systems. This explains why individuals with one lifestyle disease inevitably develop others in sequence.

Consider diabetes mellitus as an example. A patient receives a diagnosis and begins treatment targeting blood glucose control. Yet this addresses only the tip of the iceberg—the visible manifestation. The deeper, systemic inflammatory process driving the disease remains active and untreated. Consequently, even with adequate glycemic control, the patient develops additional inflammatory-mediated conditions: hypertension, hypothyroidism, myocardial infarction, stroke, and others.

The conventional approach of treating individual diseases in isolation fails to interrupt the underlying inflammatory cascade. Without addressing the root inflammatory burden, the progression from one lifestyle disease to the next becomes nearly inevitable—a perpetual loop of escalating pathology.

Paradigm Shift: Targeting Inflammation

Future therapeutic frameworks should prioritize anti-inflammatory strategies. Early intervention will mitigate the negative influence of driving factors.

- Move from glucose-centric to inflammation-centric diabetes care.
- Regularly assess inflammatory biomarkers (hs-CRP, IL-6) alongside traditional metrics.
- Integrate structured lifestyle prescriptions—dietary guidance, physical activity, smoking cessation—as foundational therapy.
- Engage patients in environmental risk reduction—pollution monitoring, sleep hygiene, stress management.
- **Research Priorities**
- Longitudinal trials measuring inflammatory endpoints, not just glycaemic outcomes.
- Exploring **gene–environment interactions** for targeted lifestyle and pharmacologic strategies.
- Evaluating **immunomodulatory treatments** and "exposome" interventions at community/public health levels.
- Identifying **biomarker trajectories** predictive of multimorbidity emergence.

CONCLUSION

Diabetes is a symptomatic endpoint within a continuum of chronic inflammation amplified by genetic predisposition and environmental exposures. Unless the underlying inflammatory milieu is addressed, diabetes acts only as a portal to additional cardiometabolic diseases—hypertension, Dyslipidemia, Myocardial Infarction and strokes.

A comprehensive treatment framework must:
1. Diagnose and monitor inflammation early.
2. Deploy lifestyle interventions as primary prevention tactics.
3. Apply pharmacologic strategies that incorporate anti-inflammatory benefits.
4. Promote societal and policy-level changes to reshape the exposome.

By treating inflammation, not merely hyperglycemia, we can truly impede the cascade of chronic diseases and improve long-term outcomes.

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