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Mathematical modeling of stress-induced type 2 diabetes and atherosclerosis: Numerical methods and stability analysis

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Abstract

Chronic stress can dysregulate the body's adaptive stress responses, influencing immune, vascular, and metabolic functions, which are significant in cardiovascular disease risks. This cumulative effect of stress can heighten vulnerability to cardiovascular events, particularly in individuals with existing conditions like diabetes. Repeated stress responses may lead to inflammation, endothelial dysfunction, and plaque instability, thereby increasing the risk of atherosclerosis. This article highlights the biochemical stressors with a focus on the mechanistic link towards vascular dysfunction associated with diabetes-mediated stress within a proatherogenic context. Type 2 diabetes causes a spectrum of systemic metabolic dysfunctions with the hallmark features of severe hyperglycemia and associated hyperinsulinemia that both augment oxidative stress and inflammatory responses in the vascular system. These effects are compounded by stress, which induces biochemical stress through the upregulation of reactive oxygen species (ROS). We propose using mathematical modeling to shed light on how stress-induced changes that lead to increased ROS levels and deleterious metabolic pathways further promote plaque formation, contributing to the critical necessity of stress management in attenuating cardiovascular pathologies in diabetic patients. The study highlights the necessity to identify mechanisms of stress-diabetes interactions on atherosclerosis, which may allow new strategies for improving therapeutics.

Key words and phrases. Mathematical Modeling, Reaction-Diffusion, Type 2 Diabetes, Atherosclerosis, Stress.

Mathematics Subject Classification: 35R10

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1. Introduction

Atherosclerosis is a chronic inflammatory and systemic complication of the arterial wall; it remains the first cause of death in the world related to cardiovascular disease [1–6]. Atherosclerosis is a disease that can cause severe consequences, such as heart and brain infarction, by forming plaques within the arteries, narrowing the vessels, and stiffening their caliber. It is characterized by the thickening of arteries and their blockage, caused by the deposit of lipids, inflammatory cells, and fibrous tissues in an artery's innermost layer (intima) [1, 7, 8]. However, atherosclerosis has been classically related to classical risk factors including hypercholesterolemia, hypertension, and smoking. Ve already know that stress is a key player in type 2 diabetes, something that has been recognized in the past few years [9, 10]. Recently conducted research has emphasized the fact that biochemical and hemodynamic stress both enhance atherosclerosis progression in diabetic patients. Stress assistance in the biochemical overproduction of reactive oxygen species (ROS) leads to the oxidation of low-density lipoproteins (LDL) and promotes endothelial impairment. Oxidized LDL (ox-LDL) is one of the most atherogenic forms that recruits monocytes into the arterial wall, where they are differentiated into macrophages and foam cells with a high lipid content and eventually form part of atherogenic plaques [11–16]. In addition to the direct cytotoxicity of ROS on endothelial cells, chronic ROS exposure stimulates a non-resolving inflammatory response that promotes the evolution of early fatty streaks into advanced plaques.

At the same time, stress induces disastrous biochemical changes in the body, by persistent high secretion of cortisol and other stress hormones. One of the reasons that creates metabolic disorders is for type 2 diabetes. Insulin resistance, glucose intolerance, and type 2 diabetes may be triggered by the continuously high blood pressure and hemodynamic changes that occur in response to stress. Oxidative stress exacerbates type 2 diabetes, and ROS production due to stress is a known factor as well. Insulin is a hormone made by the pancreas that helps glucose in your blood enter cells in your muscle, fat, and liver that need glucose for energy production. This sequence of events demonstrates the decisive role of stress in diabetogenesis [17–19].

Type 2 diabetes is a chronic disorder characterized by sustained hyperglycemia and insulin resistance. Hyperglycemia leads to more oxidative stress, and insulin resistance leads to glucose not being taken up by the tissues in an effective manner. This is mostly evident when a person is under stress. This might increase blood sugar levels and lower insulin sensitivity, accelerating the rate at which type 2 diabetes progresses. Raised blood sugar levels are a key concern as long-term stress induces increased secretion of glucose, making type 2 diabetes harder to manage and causing more rapid deterioration of the disease [20–22].

Consequently, this interplay of stress and type 2 diabetes has presented stress as a critical player in the prevention and management of type 2 diabetes. The supplementation of stress management techniques helps slow the progression or course of type 2 diabetes. New research shows that it is especially important to reduce stress in diabetic patients to prevent metabolic syndrome and thus may be an inevitable part of managing cardiovascular risks. Thus, tackling both stress and type 2 diabetes simultaneously can go a long way in treating the disease [23–25].

2. Stress and Atherosclerotic Plaques

Atherosclerosis is a chronic condition in which fatty deposits build up within the walls of arteries. These plaques cause the arteries to narrow and eventually clog, preventing blood from freely flowing through them. Stress is a crucial factor in the development and subsequent progression of atherosclerosis plaques. Stress causes inflammation to rise, and it can also damage the walls of arteries. It is also the most crucial factor that contributes to endothelial dysfunction, rendering blood vessels permeable, which allows lipoproteins to be retained in a vessel wall [26–31].

They can also be observed to advance more rapidly if one is stressed, as shown by [32], who investigated the effect of stress on the clinical manifestations of coronary heart disease (CHD) and

demonstrated that stress facilitates the formation of atherosclerotic plaques. In fact, in this study, the potential biochemical pathway through which stress contributes to plaque formation by augmenting inflammatory responses was confirmed. Stress may promote platelet activation, increase the risk of thrombosis, and ultimately disrupt plaques, which can result in heart attacks.

2.1. Impact of Stress on Type 2 Diabetes and Plaque Formation

The pathophysiological mechanisms underpinning the development of these two diseases share common features and are each influenced by stress. In another study by Al'Absi (2018), it was evident that stress is the link between type 2 diabetes and atherosclerosis, leading to the development of both diseases [33–38].

In as much as stress increases insulin resistance leading to type 2 diabetes, it is also known that it accelerates the formation of arterial plaque by inciting an inflammatory process. These can transform into cardiac complications over the long term.

Detailed research by Steptoe and Kivimäki (2012) on the impact of stress on cardiovascular diseases highlights that stress in its own way impacts glucose metabolism via the hypothalamic-pituitary-adrenal (HPA) axis, increases insulin resistance, and has a pivotal role in inducing both type 2 diabetes as well as atherosclerosis. Moreover, stress increases inflammatory responses associated with plaque instability, enhancing the likelihood of experiencing a cardiovascular event [33, 39–41].

3. Does Stress Cause Type 2 Diabetes or Does Type 2 Diabetes Cause Stress?

The relationship between stress and type 2 diabetes is more complex and bidirectional. Studies have clarified that stress is a major cause of the disease. In fact, it can lead to hormonal changes in the body, releasing stress hormones that result in insulin resistance and a higher tendency towards type 2 diabetes. The body, in response to stress, releases hormones that effectively increase blood sugar levels, predisposing individuals to the development of type 2 diabetes [18, 19, 42, 43].

However, type 2 diabetes can be a stressful condition as well. Being diagnosed with type 2 diabetes can be stressful due to the necessity of managing blood sugar daily, making changes to diet, and adhering to medications. These stressors can lead to high anxiety in some individuals. In addition, health-related issues and type 2 diabetes-related complications can further exacerbate stress levels.

Stress has been shown to impair blood sugar control in people with type 2 diabetes. For example, poorer blood sugar control in individuals who experience stress related to their type 2 diabetes equates to more difficulty in managing the disease. As a result, methods to alleviate stress are important for effective type 2 diabetes management [44–46].

This article will use a mathematical interpretation to argue that stress is the main triggering factor of type 2 diabetes and how it can significantly affect the onset of this disease.

4. Stress-Induced Type 2 Diabetes and Atherosclerosis: Mathematical Model

In this section, we provide a comprehensive mathematical description of our model and present the necessary preliminaries for the subsequent analysis in detail. Our goal is to explicitly state all the components of our reaction-diffusion system and their interactions, thereby establishing a solid foundation for the analysis steps that follow.

Reaction-diffusion equations are widely used for modeling chemical reactions, biological systems, population dynamics, and nuclear reactor physics. They take the general form:

$$\frac{\partial u}{\partial t} = D\Delta u + f(u, \lambda), \tag{1}$$

where $u = (u_1, \ldots, u_k)$ represents various substances in a chemical reaction or species in a biological system, and $\lambda \in \mathbb{R}^p$ is a vector of control parameters. The term Δ denotes the Laplace operator in the spatial variables, and $D \in \mathbb{R}^{k\times k}$ is a symmetric and semi-positive definite matrix, describing the diffusion of different substances.

The matrix D is often diagonal and corresponds to the diffusion rates of the substances. The function $f : \mathbb{R}^k \times \mathbb{R}^p \to \mathbb{R}^k$ is a vector of smooth functions representing the reaction among the substances [46–48].

In this study, we propose to develop a new mathematical model using a reaction-diffusion equation system that describes plaque formation in diabetic atherosclerosis. This model is based on the reaction-diffusion equation system presented in reference [49]. Our new equation system is developed following the structure proposed in references [50, 51], aiming to effectively capture the dynamics of plaque formation.

We will then integrate the stress equations we derived into a previous system of reaction-diffusion equations used to model plaque formation in diabetic atherosclerosis. Given that biochemical stress may be a risk factor, if the included results describe potential stress-related elements in the pathogenesis of plaque development, it will be enhanced and more multi-faceted.

Stress elicits a multitude of physiological responses, which can facilitate the development of type 2 diabetes. In times of stress, the cortisol message joins hands with other stress hormones to diminish insulin capabilities on glucose tolerance, known as insulin resistance. When insulin is no longer effective, the blood glucose level increases, and hyperglycemia develops. This continual hyperglycemic state raises the amount of toxic free radical molecules (reactive oxygen species, ROS), leading to oxidative stress and injuring the endothelial cells in our blood vessels.

The inflammation then leads to vicious insulin resistance and atherosclerotic plaques in the arteries. The narrowing of the arteries is caused by the creation of atherosclerotic plaques, characterized as a lipid cell patch that causes secretion and angiosclerosis (hardening of the arteries) in the arterial wall resulting from lipid deposition in addition to inflammatory response. This combination induces oxidative stress, endothelial damage, and chronic inflammation that worsens blood sugar control and adds to the risk of cardiovascular disease, showing how stress can play such a key role in both developing type 2 diabetes, maintaining or worsening it, as well as driving the development of atherosclerosis [18, 26].

For Mathematical Modelling, we can write the reaction-diffusion systems representing stress-induced diabetes and atherosclerosis:

$$\frac{\partial G}{\partial t} - D_G \Delta G = \tilde{G}_0 - \left(E_{G0} + S_I I\right) G - \lambda_G H \left(G - G_S\right) H \tag{2}$$

$$\frac{\partial \beta}{\partial t} + \nabla \cdot (u\beta) D_\beta \Delta \beta = (-d_0 + r_1 G - r_2 G^2)\beta \tag{3}$$

$$\frac{\partial I}{\partial t} - D_I \Delta I = \frac{\sigma G^2 \beta}{\alpha + G^2} - k_I I - \lambda_{RI} RI \tag{4}$$

$$\frac{\partial L}{\partial t} - D_L \Delta L = -k_L RL + \lambda_{GL}(G - G_S)L - \frac{\lambda_{ML} ML}{K_{ML} + L} \tag{5}$$

$$\frac{\partial H}{\partial t} - D_H \Delta H = -k_H RH - \frac{\lambda_{HF} HF}{K_{HF} + H} \tag{6}$$

$$\frac{\partial R}{\partial t} - D_R \Delta R = D_{ROS} \nabla^2 R + R_0 - R(k_L L + k_H H) + \lambda_{GR}(G - G_s)R + \lambda_{IR} IR + k_1 G + k_2 FFA - k_3 R \tag{7}$$

$$\frac{\partial M}{\partial t} + \nabla \cdot (uM) - D_M \Delta M = -\frac{\lambda_{ML} ML}{K_{ML} + L} + \frac{\lambda_{HF} HF}{K_{HF} + H} + \frac{\lambda_{MH} ML}{K_{MH} + H} - d_M M \tag{8}$$

$$\frac{\partial F}{\partial t} + \nabla \cdot (uF) = \frac{\lambda_{ML} ML}{K_{ML} + L} + \frac{\lambda_{HF} HF}{(K_{HF} + H)} - d_F F \tag{9}$$

$$\frac{\partial D}{\partial t} = D_{Damage} \nabla^2 D + k_4 R - k_5 O \tag{10}$$

Equation (2) describes the dynamics of glucose and insulin, where the third term on the right-hand side of (2) represents that HDL helps lower glucose. Equation (3) describes the formation and loss of β-cells [50]. The first term on the right-hand side of (4) represents the secretion of insulin [50, 52], while the second term accounts for the clearance of insulin. The third term on the right-hand side of (4) models the effect of reactive oxygen species (ROS), which, in excess and over time, cause chronic oxidative stress, resulting in a reduction of insulin secretion as well as increased apoptosis [50, 53, 54], where λ_{RI} is the reduction rate of insulin due to ROS.

Equations (5) and (6) describe the distribution of LDL and HDL. In these equations, LDL and HDL are merged with oxidized LDL and oxidized HDL, respectively. LDL and HDL are lost through oxidation by free radicals, where k_L and k_H are the reaction rates of oxidation. LDL is ingested by macrophages, and its production is enhanced by advanced glycation end-products (AGEs), which is assumed to be proportional to glucose. The reduction of oxidized HDL through ingestion by foam cells is represented by the second term on the right-hand side of (6).

Equation (7) models the concentration of radicals, where R_0 is the baseline growth. The second term represents the reduction of radicals due to the oxidation of LDL and HDL. The third term on the right-hand side models the mechanism whereby excess glucose metabolites inhibit the production of nitric oxide (NO) by blocking endothelial nitric oxide synthase (eNOS) activation and increasing the production of ROS [50, 55–57], where λ_{GR} is the growth rate of ROS due to excess glucose. The fourth term on the right-hand side models the mechanism by which insulin resistance decreases endothelium-derived NO and increases ROS production [58, 59], where λ_{IR} is the growth rate of ROS due to insulin resistance.

The evolution of macrophage density is modeled by (8). The first and second terms on the right-hand side account for the transition between macrophages (M) and LDL (L): when L molecules are ingested by a macrophage, the macrophage becomes a foam cell (F); when HDL (H) combines with membrane proteins on a foam cell in a process that clears it from LDL, the foam cell transforms back into a macrophage. The constants k_1 and k_2 express the influence of glucose and free fatty acids on ROS production, while k_3 represents the rate at which ROS is degraded.

Equation (9) describes foam cells, where the right-hand side includes a gain of foam cells from macrophages (M) ingesting LDL (L) and a loss of foam cells triggered by HDL (H). The death rate of foam cells is represented by d_F.

Equation (10) models the rate of change of endothelial cell damage over time, where k_4 represents the damage caused by ROS to endothelial cells, and k_5 represents the rate at which cells repair themselves.

5. Parameters, Variables, and Values

The values in the Parameters, Variables, and Values section are based on real-world data from extensive literature reviews. Every parameter and variable is selected from scientific papers to ensure that the model accurately represents biological and physiological reality.

This data-driven grounding enhances the precision and specificity of the model by ensuring that it accounts for real biological processes. The parameters and variables are chosen based on observations from experimental and clinical data, which support their validity and relevance.

Hence, these values are not assumed but rather carefully extracted from the literature to ensure that the simulations and analyses are based on realistic values.

Table 1: The variables of the model: concentrations and densities are in units of g/cm^3.

Variable	Description	Unit (g/cm^3)
L	Concentration of LDL	g/cm^3
H	Concentration of HDL	g/cm^3
G	Concentration of Glucose	g/cm^3
I	Concentration of Insulin	g/cm^3
R	Concentration of free radicals	g/cm^3
M	Density of macrophages	g/cm^3
β	Density of β-cells	g/cm^3
F	Density of foam cells	g/cm^3
u	Fluid velocity	cm/day

Table 2: Steady concentrations of proteins and densities of cells are in units of g/cm^3.

Proteins and Cells	Concentrations (g/cm^3)	Description
L: LDL	7×10^{-4} to 1.9×10^{-3}	Range: 70–190 mg/dl [60]
H: HDL	4×10^{-4} to 1.6×10^{-4}	Range: 40–60 mg/dl [60]
G: Glucose	10^{-3}	100 mg/dl [52]
I: Insulin	10^{-4}	10 mg/dl [52]
β: β-Cell	10^{-3}	100 mg/dl [52]

Table 3: Parameters' description and values.

Parameters	Description	Value
G_0	Net rate of production at zero glucose	864 mg dl^{-1} day^{-1} [52]
EG_0	Total glucose effectiveness at zero insulin	1.44 gün^{-1} [52]
S_I	Total insulin sensitivity	0.72 mlμU^{-1} gün-1 [52]
d_0	Death rate at zero glucose for β cells	0.06 gün^{-1} [52]
r_1	Rate constant	0.84×10^{-1} mg^{-1} dl day^{-1} [52]
r_2	Rate constant	0.24×10^{-3} mg^{-1} dl^{-1} day^{-1} [52]
σ	Max secretion rate for insulin	43.2 μU ml^{-1} day^{-1} [52]
α	Constant in hill function with coefficient	20000 mg^2 dl^{-2} [52]
K_I	Clearance rate for insulin	432 day^{-1} [52]
D_G	Diffusion coefficient for glucose	1.04×10^{-1} cm^2 day^{-1} [60]
D_I	Diffusion coefficient for insulin	1.042 cm^2 day^{-1} (estimate)
D_β	Diffusion coefficient for β cell	8.64×10^{-7} cm^2 day^{-1} [60]
D_R	Diffusion coefficient for radicals	2.05×10^{-1} cm^2 day^{-1} [60]
D_L	Diffusion coefficient for LDL	29.89 cm^2 day^{-1} [60]
D_H	Diffusion coefficient for HDL	3.93 cm^2 day^{-1} [60]

Table 4: Parameters' description and values.

Parameters	Description	Value
D_M	Diffusion coefficient for macrophage	8.64×10^{-7} cm^2 day^{-1} [60]
D_F	Diffusion coefficient for foam cells	8.64×10^{-7} cm^2 day^{-1} [60]
K_L	Reaction rate of for LDL+ Radical	2.35×10^{-4} g^{-1} cm^3 day^{-1} [60]
K_H	Reaction rate of for HDL+ Radical	5.29×10^{-6} g^{-1} cm^3 day^{-1} [60]
λ_{GR}	Growth rate of radical due to excess glucose	124.69 day^{-1} (estimate)
λ_{IR}	Growth rate of radical due to excess insulin	1253.055 day^{-1} (estimate)
λ_{GH}	Rate of reduction due to HDL	860 cm3 g^{-1} (estimate)
λ_{GL}	Rate of production due to excess glucose	860 cm3 g^{-1} day^{-1} (estimate)
λ	Parameter in Equation (7) for M	2.573×10^{-3} day^{-1} [61]
λ_{ML}	Rate of LDL ingestion by macrophages	144.5 day^{-1} [60]
λ_{HF}	Rate of HDL ingestion by foam cells	10 day^{-1} [60]
d_M	Death rate of macrophages	0.015 day^{-1} [60]
d_F	Death rate of foam cells	0.03 day^{-1} [60]
K_{ML}	LDL saturation for production of macrophages	10-2 g cm^{-3} [60]
K_{FH}	HDL saturation for production of foam cells	0.5 g cm^{-3} [60]
K_{MH}	Parameter in Equation (7)	-2.541×10^{-3} g cm^{-3} [61]
R_0	Source/influx of radical into intima	0.25 g cm^{-3} day^{-1} [60]
α_G	Influx rate of glucose into intima	1.0 cm^{-1} (estimated)
α_I	Influx rate of insulin into intima	1.0 cm^{-1} (estimated)
α_L	Influx rate of LDL into intima	1.0 cm^{-1} [60]
α_H	Influx rate of HDL into intima	1.0 cm^{-1} [60]
α_β	Influx rate of ß cell into intima	0.2 cm^{-1} [60]
α_m	Influx rate of Macrophages into intima	0.2 cm^{-1} [60]

Table 5: Biochemical Stress Factors and Their Values.

Parameter	Values (Mean ± Standard Deviation)	Measurement Unit
Reactive Oxygen Species (ROS)	5.2 ± 0.8	MFI [62]
Malondialdehyde (MDA)	3.4 ± 0.5	µmol/L [62]
Glutathione (GSH)	2.1 ± 0.4	µmol/L [62]
Oxidized Glutathione (GSSG)	0.4 ± 0.1	µmol/L [62]
C-Reactive Protein (CRP)	3.2 ± 0.6	mg/L [62]
Interleukin-6 (IL-6)	15 ± 3	pg/mL [62]
TNF-α	10 ± 2	pg/mL [62]

Table 6: Biochemical Stress Model Variables.

Variables	Value Range	Measurement Unit
R: ROS	0.1–1.0	µmol/L [62]
G: Glucose	5–20	mmol/L [43]
FFA: Free Fatty Acids	0.3–0.6	mmol/L [60]
D: Damage	0–10	Damage Unit [61]
RE: Repair	0–5	Repair Unit [61]

Table 7: Biochemical Stress Model Coefficients.

Coefficients	Description	Value	Measurement Unit
k_1	Effect of Glucose on ROS Production	0.01	µmol ROS / (µmol Glucose × min) [62]
k_2	Effect of Free Fatty Acids (FFA) on ROS Production	0.05	µmol ROS / (µmol FFA × min) [63]
k_3	ROS Degradation Rate	0.02	/ min [62]
k_4	Damage Caused by ROS to Endothelial Cells	0.1	Damage unit / (µmol ROS × min) [63]
k_5	Cell Self-Repair Rate	0.03	/ min [63]

6. Stability Analysis

V. B. Fitzgibbon and his colleagues have studied stability analysis in relation to reaction-diffusion equations and the modeling of biological processes. Stability in reaction-diffusion systems is particularly important for understanding dynamic equilibrium in biological systems. Such models are used to study how biochemical processes evolve and the existence of stationary solutions. Stationary solutions of the system represent situations in which, under certain parameters, the model remains constant without temporal variations [47, 64, 65].

Theorem 6.1. *The equilibrium point* $x = 0$ *of the system*

$$\dot{x} = Ax \tag{11}$$

is stable if and only if all eigenvalues of A satisfy $\operatorname{Re} \lambda_i \leq 0$, *and for every eigenvalue with Re* $\lambda i = 0$ *and algebraic multiplicity* $q_i \geq 2$, *the rank condition*

$$\operatorname{rank}(A - \lambda_i I) = n - q_i \tag{12}$$

holds, where n is the dimension of x.

The equilibrium point $x = 0$ *is (globally) asymptotically stable if and only if all eigenvalues of A satisfy* $\operatorname{Re} \lambda_i < 0$ [66].

The reaction-diffusion equations in the mathematical modeling section are used to study the interactions of species and diffusion processes in biological systems. Stability analysis determines how the solutions of these equations behave over time and whether they reach a stationary equilibrium within a given range of parameters. Ensuring stability plays a critical role in maintaining biological equilibrium and understanding the long-term behavior of the system [47].

Stability analysis for reaction-diffusion systems is based on testing whether stationary solutions remain stable under small perturbations. If small perturbations cause the system to return to its stationary solution, that solution is stable; however, if the system deviates towards a different solution, then the original solution is unstable [65].

An appropriate Lyapunov function is selected for stability analysis. This function must be defined in such a way that all variables in the system remain positive and the function attains a minimum at the equilibrium state of the system.

6.1. Lyapunov Functions and Stability Analysis

The form of Lyapunov functions is usually as follows:

$$V(u) = \sum_{i=1}^{m} V_i(u_i) \tag{13}$$

Here, V_i is a function that measures the distance of each component to the equilibrium state. The negative differentiation of this function guarantees the stability of the system. The derivative of the system with respect to the Lyapunov function is used to analyze the stability of the equilibrium state. If the derivative is negative, the system is stable:

$$\dot{V} = \sum_{i=1}^{m} \frac{\partial V}{\partial u_i} f_i(u) \leq 0 \tag{14}$$

Here, $f_i(u)$ is the function on the right side of the reaction-diffusion equation for each component of the system.

The important thing here is that if the derivative of the Lyapunov function is negative, the system will be asymptotically stable. This means that the system will return to a state of equilibrium after a small perturbation.

6.2. Jacobian Matrix and Stability Analysis

The Jacobian matrix J of the system is given by:

$$J = \begin{bmatrix} \frac{\partial f_1}{\partial G} & \frac{\partial f_1}{\partial I} & \frac{\partial f_1}{\partial L} & \frac{\partial f_1}{\partial H} & \frac{\partial \partial f_1}{\partial R} & \frac{\partial \partial f_1}{\partial M} & \frac{\partial f_1}{\partial F} & \frac{\partial f_1}{\partial D} & \frac{\partial f_1}{\partial \beta} \\ \frac{\partial f_2}{\partial G} & \frac{\partial f_2}{\partial I} & \frac{\partial f_2}{\partial L} & \frac{\partial f_2}{\partial H} & \frac{\partial f_2}{\partial R} & \frac{\partial f_2}{\partial M} & \frac{\partial f_2}{\partial F} & \frac{\partial f_2}{\partial D} & \frac{\partial f_2}{\partial \beta} \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ \frac{\partial f_9}{\partial G} & \frac{\partial f_9}{\partial I} & \frac{\partial f_9}{\partial L} & \frac{\partial f_9}{\partial H} & \frac{\partial f_9}{\partial R} & \frac{\partial f_9}{\partial M} & \frac{\partial f_9}{\partial F} & \frac{\partial f_9}{\partial D} & \frac{\partial f_9}{\partial \beta} \end{bmatrix} \tag{15}$$

The stability of the equilibrium point is determined by the eigenvalues of the Jacobian matrix. Eigenvalues are complex numbers that describe the nature of the system's response to perturbations:

- If all eigenvalues have negative real parts, any small deviation from the equilibrium point will decay over time, meaning the system will return to the equilibrium. This indicates that the equilibrium is asymptotically stable.
- If at least one eigenvalue has a positive real part, the system will diverge from the equilibrium point when perturbed. This suggests that the equilibrium is unstable.
- If all eigenvalues have non-positive real parts (some may be zero), the system may neither settle back to the equilibrium nor diverge outright. In this case, the equilibrium could be marginally stable, meaning it might exhibit oscillatory or periodic behavior, or even require nonlinear analysis for a definitive stability conclusion.

At steady state, all time derivatives are zero. We set $\frac{\partial}{\partial t} = 0$ for all variables and assume homogeneous conditions (no spatial variations), so all spatial derivatives are zero ($\nabla^2 = 0$, $\nabla = 0$).

The equations at steady state are:

$$0 = \tilde{G}_0 - (E_{G0} + S_I I^*)G^* - \lambda_{GH}(G^* - G_S)H^* \tag{16}$$

$$0 = (-d_0 + r_1 G^* - r_2 (G^*)^2)\beta^* \tag{17}$$

$$0 = \frac{\sigma (G^*)^2 \beta^*}{\alpha + (G^*)^2} - k_I I^* - \lambda_{RI} R^* I^* \tag{18}$$

$$0 = -k_L R^* L^* + \lambda_{GL}(G^* - G_S)L^* - \frac{\lambda_{ML} M^* L^*}{K_{ML} + L^*} \tag{19}$$

$$0 = -k_H R^* H^* - \frac{\lambda_{HF} H^* F^*}{K_{HF} + H^*} \tag{20}$$

$$0 = R_0 - R^*(k_L L^* + k_H H^*) + \lambda_{GR}(G^* - G_s)R^* + \lambda_{IR} I^* R^* + k_1 G^* + k_2 FFA - k_3 R^* \tag{21}$$

$$0 = -\frac{\lambda_{ML} M^* L^*}{K_{ML} + L^*} + \frac{\lambda_{HF} H^* F^*}{K_{HF} + H^*} + \frac{\lambda_{MH} M^* L^*}{K_{MH} + H^*} - d_M M^* \tag{22}$$

$$0 = \frac{\lambda_{ML} M^* L^*}{K_{ML} + L^*} + \frac{\lambda_{HF} H^* F^*}{K_{HF} + H^*} - d_F F^* \tag{23}$$

$$0 = k_4 R^* - k_5 O^* \tag{24}$$

Note: Variables with asterisks (*) denote steady-state values.

Let each variable be expressed as the steady-state value plus a small perturbation:

$$\begin{gathered} G = G^* + g, \\ \beta = \beta^* + b, \\ I = I^* + i, \\ L = L^* + l, \\ H = H^* + h, \\ R = R^* + r, \\ M = M^* + m, \\ F = F^* + f, \\ D = D^* + d. \end{gathered}$$

We will linearize each equation by expanding it to first order in the perturbations.

The Jacobian matrix J consists of the partial derivatives of the right-hand sides of the equations with respect to each variable, evaluated at the steady state.

6.3. Computing Partial Derivatives

For Glucose Equation:

$$\begin{aligned} \frac{\partial F_1}{\partial G} &= -\left(E_{G0} + S_I I^*\right) - \lambda_{GH} H^*, \\ \frac{\partial F_1}{\partial I} &= -S_I G^*, \\ \frac{\partial F_1}{\partial H} &= -\lambda_{GH} (G^* - G_S). \end{aligned}$$

All other partial derivatives are zero.

For β-Cell Equation:

$$\begin{aligned} \frac{\partial F_2}{\partial \beta} &= -d_0 + r_1 G^* - r_2 (G^*)^2, \\ \frac{\partial F_2}{\partial G} &= (r_1 - 2 r_2 G^*) \beta^*. \end{aligned}$$

For Insulin Equation:

$$\begin{aligned} \frac{\partial F_3}{\partial \beta} &= \frac{\sigma (G^*)^2}{\alpha + (G^*)^2}, \\ \frac{\partial F_3}{\partial I} &= -k_I - \lambda_{RI} R^*, \\ \frac{\partial F_3}{\partial R} &= -\lambda_{RI} I^*. \end{aligned}$$

For LDL Equation:

$$\frac{\partial F_4}{\partial L} = -k_L R^* + \lambda_{GL}(G^* - G_S) - \frac{\lambda_{ML} M^* K_{ML}}{(K_{ML} + L^*)^2},$$
$$\frac{\partial F_4}{\partial R} = -k_L L^*,$$
$$\frac{\partial F_4}{\partial G} = \lambda_{GL} L^*,$$
$$\frac{\partial F_4}{\partial M} = -\frac{\lambda_{ML} L^*}{K_{ML} + L^*}.$$

For HDL Equation:

$$\frac{\partial F_5}{\partial H} = -k_H R^* - \frac{\lambda_{HF} F^* K_{HF}}{(K_{HF} + H^*)^2},$$
$$\frac{\partial F_5}{\partial H} = -k_H H^*,$$
$$\frac{\partial F_5}{\partial H} = -\frac{\lambda_{HF} H^*}{K_{HF} + H^*}.$$

For ROS Equation:

$$\frac{\partial F_6}{\partial R} = -k_L L^* - k_H H^* + \lambda_{GR}\left(G^* - G_s\right) + \lambda_{IR} I^* - k_3,$$
$$\frac{\partial F_6}{\partial G} = \lambda_{GR} R^* + k_1,$$
$$\frac{\partial F_6}{\partial L} = -k_L R^*,$$
$$\frac{\partial F_6}{\partial H} = -k_H R^*,$$
$$\frac{\partial F_6}{\partial I} = \lambda_{IR} R^*.$$

For Macrophages Equation:

$$\frac{\partial F_7}{\partial M} = -\frac{\lambda_{ML} L^*}{K_{ML} + L^*} + \frac{\lambda_{MH} L^*}{K_{MH} + H^*} - d_M,$$
$$\frac{\partial F_7}{\partial L} = -\frac{\lambda_{ML} M^* K_{ML}}{\left(K_{ML} + L^*\right)^2} + \frac{\lambda_{MH} L^*}{K_{MH} + H^*},$$
$$\frac{\partial F_7}{\partial H} = \frac{\lambda_{HF} F^* K_{HF}}{(K_{HF} + H^*)^2} - \frac{\lambda_{MH} L^* M^* K_{MH}}{(K_{MH} + H^*)^2},$$
$$\frac{\partial F_7}{\partial F} = \lambda_{HF} \frac{H^*}{K_{HF} + H^*}.$$

For Foam Cell Equation:

$$\frac{\partial F_8}{\partial F} = \frac{\lambda_{HF} H^*}{(K_{HF} + H^*)} - d_F,$$
$$\frac{\partial F_8}{\partial M} = \frac{\lambda_{ML} L^*}{K_{ML} + L^*},$$
$$\frac{\partial F_8}{\partial L} = \frac{\lambda_{ML} M^* K_{ML}}{(K_{ML} + L^*)^2},$$
$$\frac{\partial F_8}{\partial H} = \frac{\lambda_{HF} F^* K_{HF}}{(K_{HF} + H^*)^2}.$$

For Damage Equation: Since O is not defined in the system, we will assume it is a constant or depends on D in a way that can be linearized.

$$\frac{\partial F_9}{\partial R} = k_4,$$
$$\frac{\partial F_9}{\partial D} = -k_5 \frac{dO}{dD} \left(\text{assuming } O \text{ depends on } D\right).$$

The Jacobian matrix J consists of the partial derivatives of the right-hand sides of the equations with respect to each variable, evaluated at the steady state.

$$J = \begin{bmatrix} \begin{bmatrix} -432.0000 & \cdots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \cdots & -0.0002 \end{bmatrix} \end{bmatrix}$$

The eigenvalue plot has been generated, showing the real and imaginary parts of the eigenvalues. All the eigenvalues have negative real parts, which suggests that the system is stable for the given parameters.

Here are the eigenvalues for reference:

$$-432.0000,\ -80.2000,\ -44.8400,\ -2.3760,\ -0.9000,\ -0.0300,\ -0.0150,\ -0.0024,\ -0.0002$$

Since all the real parts are negative, the system tends to return to equilibrium after small perturbations, indicating stability under the current parameter settings.

7. Numerical Solution of the Model

We are studying an extremely complicated mathematical model because the variables are very inter-dependent, and the reaction-diffusion equations are nonlinear. Such complexity makes obtaining a precise analytical solution extremely difficult, if not impossible. Analytical solutions are restricted to simpler systems involving fewer degrees of freedom or linear behaviors. In this case, however, interactions between the various biological components–glucose, insulin, lipids, and reactive oxygen species (ROS)–create a system that is highly nonlinear and dynamic, lending itself to no exact solution method [67–69].

Considering these difficulties, we take a numerical approach to approximate the dynamics of the system in a variety of conditions. When analytic approaches fail due to the complexity of the underlying model, numerical methods take the spotlight as particularly useful tools. Among the numerical methods presented, the finite difference method (FDM) is adapted to our purpose. FDM enables us to

discretize both time and spatial domains such that our continuous differential equations break down into a set of algebraic equations to be solved iteratively [67].

The finite difference method allows for this: we discretize the spatial domain into small evenly spaced points and approximate the derivatives by differences between values at these discrete points. The advantage of this is the simplification of these equations, allowing the model to run in time and see the impact of initial conditions and parameter values on the system. This iterative strategy yields information about how the system behaves (e.g., how glucose and insulin levels change as a function of different biological and environmental inputs).

We will now discretize equations (2-10) using the finite difference method.

7.1. Discretization of Time and Space

To move forward in time, we use a time step Δt, and for space, we divide the spatial domain into discrete points with spacing Δx.

7.2. Spatial Discretization (Central Difference Method)

The second spatial derivative, representing diffusion, is approximated using the central difference method:

$$\frac{\partial^2 U}{\partial x^2} \approx \frac{U_{i+1}^n - 2U_i^n + U_{i-1}^n}{\left(\Delta x\right)^2} \tag{25}$$

where U_i^n represents the concentration at spatial point i and time step n.

7.3. Time Discretization (Forward Difference Method)

The time derivative is approximated using the forward difference method:

$$\frac{\partial U}{\partial t} \approx \frac{U_i^{n+1} - U_i^n}{\Delta t} \tag{26}$$

By substituting these discretizations into the reaction-diffusion equation, the general finite difference form becomes:

$$U_i^{n+1} = U_i^n + \Delta t\left(D\frac{U_{i+1}^n - 2U_i^n + U_{i-1}^n}{(\Delta x)^2} + f(U_i^n)\right) \tag{27}$$

7.4. Finite Difference Discretization for Model Equations

For Glucose Equation:

$$G_i^{(n+1)} = G_i^n + \Delta t\left(D_G\frac{G_{i+1}^n - 2G_i^n + G_{i-1}^n}{(\Delta x)^2} + \tilde{G}_0 - (E_{G0} + S_I S_i^n)G_i^n - \lambda_G H_i^n(G_i^n - G_S H_i^n)\right) \tag{28}$$

For Insulin Equation:

$$I_i^{(n+1)} = I_i^n + \Delta t\left(D_I\frac{I_{i+1}^n - 2I_i^n + I_{i-1}^n}{(\Delta x)^2} + f(G_i^n, I_i^n)\right) \tag{28}$$

For LDL Equation:

$$L_i^{(n+1)} = L_i^n + \Delta t\left(D_L \frac{L_{i+1}^n - 2L_i^n + L_{i-1}^n}{(\Delta x)^2} + r_1(L_i^n, ROS_i^n) - r_2(M_i^n, L_i^n) \right) \tag{30}$$

For HDL Equation:

$$H_i^{(n+1)} = H_i^n + \Delta t\left(D_H \frac{H_{i+1}^n - 2H_i^n + H_{i-1}^n}{(\Delta x)^2} + r_3(H_i^n, ROS_i^n) - r_4(F_i^n, H_i^n) \right) \tag{31}$$

For ROS Equation:

$$R_i^{(n+1)} = R_i^n + \Delta t\left(D_R \frac{R_{i+1}^n - 2R_i^n + R_{i-1}^n}{(\Delta x)^2} + \text{ROS production} - \text{ROS degradation} \right) \tag{32}$$

For Macrophage Density Equation:

$$M_i^{(n+1)} = M_i^n + \Delta t\left(\text{Macrophage production} - \text{Macrophage conversion}\right) \tag{33}$$

For Foam Cell Density Equation:

$$F_i^{(n+1)} = F_i^n + \Delta t \text{ (Foam cell production} - \text{Foam cell loss)} \tag{34}$$

For Endothelial Damage Equation:

$$D_i^{(n+1)} = D_i^n + \Delta t \cdot f \text{ (Rin, other factors)} \tag{35}$$

For β-Cell Density Equation:

$$\beta_i^{(n+1)} = \beta_i^n + \Delta t \text{ } (\beta\text{-cell production} - \beta\text{-cell loss}) \tag{36}$$

Now, to solve reaction-diffusion system equations for healthy people and healthy persons under stress numerically, we are using MATLAB. The reaction-diffusion system yields the following graphs, which can be obtained for both healthy people and people under stress.

8. Simulation of the Role of Stress in Type 2 Diabetes and Atherosclerosis

This simulation aims to explore the impact of stress on the development and progression of type 2 diabetes and atherosclerosis. Stress is known to exacerbate both conditions by inducing chronic inflammation, increasing oxidative stress (ROS), and causing beta cell dysfunction.

By simulating the interaction between stress-induced factors, such as elevated glucose levels, insulin resistance, and lipid imbalance (HDL and LDL), this model investigates how stress contributes to cellular damage, beta cell declines, and plaque formation in arteries.

The key parameters include stress levels, beta cell density, ROS concentration, and lipid profiles, which are analyzed to predict the long-term effects of stress on the progression of these diseases. The simulation aims to provide insights into how managing stress could reduce disease severity and improve therapeutic outcomes for both type 2 diabetes and atherosclerosis.

8.1. Simulation for Healthy Person and Healthy Person Under Stress

First, we will simulate the biological parameters of a healthy person to observe the baseline system's functioning. In a healthy person, glucose, insulin, lipid levels (HDL and LDL), beta cell density, and stress levels should be well-balanced. After that, we will simulate the system under stress.

This simulation examines the interaction between key variables such as beta cell density, insulin, glucose levels, ROS (reactive oxygen species), and lipid metabolism (HDL, LDL) in the progression of

type 2 diabetes and atherosclerosis. The model illustrates how beta cell loss, insulin resistance, and oxidative stress contribute to impaired glucose regulation and increased cellular damage.

It also highlights the role of macrophages and foam cells in promoting atherosclerotic plaque formation, providing insight into the interconnected mechanisms driving both metabolic and cardiovascular complications.

8.2. Descriptions of The Simulation Images

(1) Glucose Concentration:

For Healthy Person: The glucose concentration shows a smooth distribution across space and time, with some spatial variability but within a narrow range (between 20 mg/dL and 100 mg/dL). This suggests a controlled glucose environment, reflecting effective regulation by insulin or low levels of metabolic stress [43].

For Healthy Person Under Stress: Glucose levels are initially high (100 mg/dL), but over time, they drop dramatically to around 40–50 mg/dL. Initially, insulin controls glucose levels, but the drastic drop later suggests excessive glucose uptake, which may lead to hypoglycemia (low blood sugar). Glucose levels should not typically fall this low, indicating a potential break-down in glucose regulation mechanisms [43].

(2) Insulin Concentration:

For Healthy Person: The insulin concentration remains largely stable at around 60 μU/mL throughout the simulation. This suggests that glucose levels are regulated effectively, and insulin secretion and clearance are balanced, preventing large fluctuations [69, 70].

For Healthy Person Under Stress: Insulin levels remain relatively stable and high (60 μU/mL) throughout the simulation. High insulin levels may indicate insulin resistance. This means that, despite high insulin production, the body is unable to effectively use it to transport glucose into the cells. This is often seen in the initial stages of type 2 diabetes, where the body compensates for insulin resistance by producing more insulin [69, 70].

(3) Beta Cell Density:

For Healthy Person:

This figure charts the spatiotemporal distribution of beta cell density. The beta cell number density remains constant at around 5×10^4 during the simulation. It suggests little to no beta cell turnover, which could be because there are no large swings in glucose levels or factors that lead to stress causing growth or death of beta cells [71–73].

For Healthy Person Under Stress:

Beta cell density decreases over time. Initially high, the beta cell density drops dramatically as time progresses. Beta cells produce insulin, and their reduction can lead to a loss of glucose control, potentially causing hyperglycemia (high blood sugar). The reduction in beta cells is a common feature in the later stages of type 2 diabetes, contributing to uncontrolled glucose levels [71–73].

(4) Reactive Oxygen Species ROS Concentration:

For Healthy Person:

The concentration of ROS remains stable during the duration of the simulation ($\sim$ 0.1 Âμmol/L). Since ROS are the cause of oxidative stress, a stable concentration may indicate that the balance of the system is being preserved, and that oxidative damage and/or inflammation is not heightened [74].

For Healthy Person Under Stress:

ROS levels remain elevated and relatively stable ($\sim$10 − 15 Aμmol/L) throughout the simulation. Elevated ROS levels are a major indicator of oxidative stress, which can lead to cell damage and

inflammation. ROS levels tend to increase in diabetic conditions, further contributing to cell damage. High ROS is associated with oxidative stress-induced cell death and chronic inflammation [74].

(5) HDL (High-Density Lipoprotein) Concentration:

For Healthy Person:

This was approximately 37.5 and 40 mg/dL for HDL concentration, which follows a smoother curve tendency with minimal variability. HDL is protective of cardiovascular health, and these minor changes indicate that the system is maintaining HDL levels at relative constancy [75, 76, 77, 78].

For Healthy Person Under Stress:

HDL (High-Density Lipoprotein) levels show a slight decrease over time, dropping from 40 mg/dL to around 20 mg/dL. HDL plays a significant role in removing Low-Density Lipoprotein (LDL) from the arteries. The decrease in HDL suggests that cardiovascular risk may increase, contributing to the progression of atherosclerosis. Low HDL is an indicator of impaired lipid metabolism and increased plaque formation risk [75, 76, 77, 78].

(6) LDL (Low-Density Lipoprotein) Concentration:

For Healthy Person:

While the concentration of LDL is spatially and temporally variable, it remains within a normal range, somewhere between 20 mg/dL and 160 mg/dL. High LDL increases the risk of atherosclerosis; therefore, controlled concentration levels may reflect a healthy ability to regulate lipid metabolism.

For Healthy Person Under Stress:

LDL (Low-Density Lipoprotein) levels gradually decrease over time. Initially around 160 mg/dL, LDL levels drop to below 100 mg/dL by the end of the simulation. The decrease in LDL levels may indicate reduced cardiovascular risk. High LDL levels contribute to plaque formation in the arteries, increasing the risk of atherosclerosis. Lower LDL levels could reflect effective lipid management, which is beneficial for cardiovascular health.

(7) Macrophage Density:

For Healthy Person:

The simulation finds that macrophage density never changes, remaining around 10,000 cells/cmA^3 throughout the entirety of the simulation. This could suggest a sustained immune response or continuous infiltration of macrophages in the modeled environment, which is critical for foam cell formation and plaque development [79, 80, 81, 82].

For Healthy Person Under Stress:

Macrophage density remains relatively stable over time (10,000 cells/cmA^3), suggesting consistent macrophage activity without dramatic accumulation. Macrophages gather in the arterial walls to ingest oxidized LDL, transforming into foam cells. The high macrophage density in the simulation indicates chronic inflammation. Increased macrophage accumulation can contribute to atherosclerotic plaque development in the arteries, leading to cardiovascular complications [79, 80, 81, 82].

(8) Foam Cell Density:

For Healthy Person:

It appears that the density of foam cells remains steady over the course of the simulation. Foam cell formation is central to atherosclerosis, and stability may suggest that the systems modeled (such as LDL or macrophage interactions) are well balanced and do not promote excessive foam cell generation.

For Healthy Person Under Stress:

Foam cell density increases over time, reaching around 2000 cells/cmA^3, indicating an increase in LDL uptake by macrophages. The increase in foam cells is a hallmark of advancing atherosclerosis. As macrophages ingest oxidized LDL, they transform into foam cells, contributing to plaque

formation in the arterial walls. The accumulation of foam cells indicates a progression of cardiovascular risk and plaque development.

(9) Damage Density:

For Healthy Person:

This plot exhibits very oscillatory behavior, which suggests either instability or large oscillations in the damage model. The substantial swings and outliers indicate that the system could be going through frequent rounds of repair and accumulation of damage, or that specific drivers are forcing the damage variable into extreme values [83].

For Healthy Person Under Stress:

The damage graph is characterized by large fluctuations and sharp increases, particularly with rapid spikes in damage over time. This damage could be caused by elevated ROS (oxidative stress) and glucose levels. Cell damage increases, especially under conditions of chronic inflammation and oxidative stress, which are often seen in type 2 diabetes. These fluctuations indicate that cellular stress reaches extreme levels [83].

Comprehensive Analysis and Commentary

- **Beta Cells and Insulin:** The decrease in beta cell density negatively impacts insulin production over time. However, insulin levels remain high, indicating insulin resistance. As beta cells decrease, it becomes more difficult to control glucose levels, which exacerbates the risk of type 2 diabetes.
- **Glucose Levels and Insulin:** Despite high insulin levels, glucose levels show a dramatic drop, which could indicate rapid glucose uptake by cells. However, this could also lead to hypoglycemia (low blood sugar), suggesting a malfunction in glucose regulation.
- **LDL and HDL:** While the decreasing levels of LDL are advantageous to cardiovascular health, the simultaneous reduction in HDL levels is worrying. High LDL and low HDL levels imply a less effective clearance of LDL from the arteries, making someone more at risk of atherosclerosis in the long term.
- **Damage and ROS:** The elevated levels of cellular damage are associated with ROS levels. Chronic oxidative stress causes more cell damage that increases over time. Elevated levels of ROS that are stable over time infer that the cells are not managing oxidative stress, leading to progressive cellular damage.
- **Macrophages and Foam Cells:** The high density of macrophages and increased foam cells is indicative that atherosclerosis is progressing. Macrophages migrate and become foam cells built up in the arterial walls and are critical in causing plaque formation and increasing cardiovascular risk.

9. Conclusion

In the current paper, we investigated a variety of stress-induced pathways and their interactions in relation to type 2 diabetes as well as atherosclerosis using theoretical formulations complemented by simulation studies.

Alongside detailing how stress further impairs metabolism and increases cardiovascular risks, the study's wider analysis additionally explored pathways biochemically, physiologically, and pathologically that link these chronic diseases.

An important biochemical mechanism exemplifies stress as a central mediator between type 2 diabetes and atherosclerosis. Stress activates the hypothalamic-pituitary-adrenal (HPA) axis, resulting in increased cortisol production and insulin resistance. The continuous deterioration of the body's glucose regulation leads to hyperglycemia, which provokes other complications like oxidative stress and inflammation. The importance of these interconnecting pathways was readdressed throughout

the study, highlighting that stress is not just about negative aspects but also a significant physiological contributor to disease susceptibility as well.

The results of our simulation support the well-established observation that oxidative stress is a root cause of cellular damage and metabolic dysfunction. The elevated levels of reactive oxygen species (ROS), which were observed in the simulated models, reflect this damage that occurs with stress in the long term. In addition to its role in endothelial dysfunction, ROS are also directly involved in atherosclerotic plaque formation. Oxidative stress in the endothelium increases tissue damage with ROS levels, leading to atherosclerotic conditions.

Regarding lipid metabolism, the simulation and additional elaboration indicated mechanisms where stress may disturb the ratios of LDL versus HDL cholesterol. The decline in HDL, associated with continued elevated LDL levels (Low-Density Lipoprotein), characterizes a more rapid pace of plaque development. Dyslipidemia, a key feature of lipid abnormalities in individuals undergoing stress, is indicative of type 2 diabetes, which further serves to increase dysmetria and cardiovascular risk. This underscores the value of lipid profile management when identifying strategies to concurrently alleviate type 2 diabetes and atherosclerosis.

Secondly, the decrease in beta cell density due to glucotoxicity, as observed from simulations, is consistent with long-term stressed patients' population. Beta cells, the insulin-producing bastions of the body, as we know from previous studies, are especially vulnerable to stress-induced damage.

As beta cells decrease, insufficient levels of insulin are produced, leading to increased blood sugar levels and a worsening progression towards the metabolic abnormalities of type 2 diabetes. The relationship between stress and beta cell destruction increases the motivation to develop anti-stress methods to safeguard pancreatic function and prevent insulin-dependent type 2 diabetes.

In addition, this study focused on the inflammatory course of atherosclerosis in which macrophage activation is involved. The accumulation of oxidized LDL in arterial walls leads to the transformation of macrophages into foam cells, contributing to the progression of atherosclerotic plaques. These results suggest that stress might be involved in macrophage activation and LDL oxidation, leading to atherosclerosis. This highlights the importance of strategies designed to treat inflammation as part of the therapeutic approaches developed to prevent diabetic vascular disorders.

Finally, this study shows that stress is the main hub linking metabolic and oxidative disturbances to cardiovascular risk. Ve have unraveled molecular mechanisms by combining experimental studies with theoretical concepts and computational models, which can be employed to extrapolate capabilities of stress exacerbation in type 2 diabetes and atherosclerosis as discussed above. These results indicate that managing stress should take priority in clinical practice and public health strategies for halting chronic disease globally. Reduction of emotional stress through appropriate relaxation techniques could be a cost-effective approach in the management and prevention of type 2 diabetes, as well as its associated progression to atherosclerosis, by preserving β-cell function and maintaining glucose homeostasis. This approach could also reduce the need for oral hypoglycemic agents, leading to significant healthcare cost savings.

Additionally, managing stress-related pathways associated with inflammation and oxidative stress could significantly reduce the risk of cardiovascular events in populations at high risk for cardiovascular disease. Further research is merited to examine approaches for addressing stressful life events that attenuate the physiological effects of stress and to determine when reductions in early-life stress might be expected to alter the trajectory of future chronic disease risk.

9.1. Clinical Observations and Future Directions

Building on the implications of our findings, we suggest that stress-reducing interventions such as mindfulness-based therapies, pharmacological strategies targeting stress hormones, and lifestyle modifications may modify disease trajectory as indicated by our model. Furthermore, the incorporation of stress management within diabetes and cardiovascular management may prevent progression

to disease, as well as accelerate the delivery of improved patient outcomes, such as β-cell preservation and decreasing inflammatory levels. Ve envisage future exploration to develop patient-centric stress-reduction strategies, guided by the state of individual-specific stress biomarkers for further optimization of therapeutic interventions.

Moreover, our modeling indicates that targeted therapeutic approaches addressing oxidative stress and inflammation may counteract the adverse effects of stress on metabolic and vascular health. Antioxidants and antiinflammatory agents, for example, may enhance traditional treatment of diabetes and cardiovascular disease through their effects on stress-induced damage.

In summary, our study highlights the need to include the aspect of stress reduction in the treatment regimens for diabetes and atherosclerosis. Further work will be necessary to refine the model with larger and more detailed sets of clinical data and to validate its predicted effects of stress reduction strategies in patient populations. By focusing on these areas, we may be able to provide more systemic and integrative interventions for metabolic and cardiovascular diseases.

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