IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

A Review On Biochemical Changes Stress Associated With Diabetes Mellitus

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Abstract:

Diabetes mellitus (DM) is a multifactorial metabolic condition marked by sustained hyperglycaemia and widespread biochemical disturbances that influence multiple organ systems. Ongoing metabolic dysregulation in diabetes disrupts carbohydrate, lipid, and protein metabolism and is closely associated with increased oxidative stress and chronic inflammation. Prolonged elevation of blood glucose enhances the production of reactive oxygen species (ROS), weakens endogenous antioxidant systems, and impairs mitochondrial function, ultimately leading to cellular and tissue injury.

Physiological and biochemical stress significantly contributes to the onset and progression of diabetes by stimulating neuroendocrine responses, including elevated secretion of cortisol and catecholamines. These hormonal changes exacerbate insulin resistance and accelerate pancreatic β-cell dysfunction. Variations in crucial biochemical indicators—such as increased lipid peroxidation, diminished antioxidant enzyme activity, accumulation of advanced glycation end products, and imbalances in stress-related hormones—play a central role in the development of chronic diabetic complications. These complications include neuropathy, nephropathy, retinopathy, and cardiovascular diseases.

A thorough understanding of the interrelationship between metabolic stress, oxidative damage, and biochemical alterations is vital for early detection and effective management of diabetes mellitus. Therapeutic strategies emphasizing optimal glycaemic regulation, stress management, antioxidant supplementation, and healthy lifestyle practices are essential in slowing disease progression and

enhancing quality of life. Comprehensive analysis of these mechanisms offers valuable insights for the advancement of targeted preventive and therapeutic interventions in diabetes care.

Keywords:

Diabetes mellitus; Stress; Biochemical changes; Hyperglycaemia; Insulin resistance; Oxidative stress; Inflammation; Neurohormonal dysregulation; Hypothalamic–pituitary–adrenal axis; Sympathetic nervous system; Cortisol; Reactive oxygen species; Endothelial dysfunction; Metabolic stress; Cardiovascular complications

Introduction:

Diabetes mellitus (DM) is a long-term metabolic disease defined by continuous hyperglycaemia arising from impaired insulin secretion, defective insulin action, or a combination of both. It has emerged as a major global public health challenge due to its increasing incidence and its close association with widespread biochemical, physiological, and cellular abnormalities.{1} In addition to disrupted glucose homeostasis, diabetes is now widely acknowledged as a condition of persistent metabolic and biochemical stress that impacts several organ systems and significantly contributes to long-term morbidity and mortality.{2}

Persistent hyperglycaemia is a hallmark biochemical abnormality in diabetes and leads to disturbances in carbohydrate, lipid, and protein metabolism. Excess intracellular glucose is diverted into alternative metabolic pathways, such as the polyol pathway, hexosamine pathway, and protein kinase C activation, resulting in excessive production of reactive oxygen species (ROS) and weakening of intrinsic antioxidant defense mechanisms.{3}{4} The resulting imbalance between oxidative burden and antioxidant protection gives rise to oxidative stress, which plays a pivotal role in diabetes-related cellular injury. Increased oxidative stress adversely affects membrane structure, enzymatic function, and gene regulation, ultimately compromising normal cellular physiology.{5}

Stress in diabetes encompasses both biochemical and neuroendocrine components. Chronic metabolic stress stimulates activation of the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system, leading to elevated levels of cortisol, catecholamines, and glucagon. These hormonal changes further aggravate insulin resistance and destabilize glycaemic control.{6} Biochemically, stress is evidenced by enhanced lipid peroxidation, oxidative modification of proteins, DNA damage, and increased formation of advanced glycation end products (AGEs). Interaction of AGEs with their specific receptors (RAGE) initiates inflammatory signalling pathways, thereby intensifying oxidative and inflammatory stress responses.{7}{8}

These biochemical disturbances are central to the pathogenesis of diabetic complications. Sustained oxidative stress and inflammation promote endothelial dysfunction, mitochondrial damage, pancreatic β-cell apoptosis, and worsening insulin resistance, linking metabolic imbalance to the development of both microvascular and macrovascular complications, including neuropathy, nephropathy, retinopathy, and

cardiovascular disease.{9} Notably, despite differences in underlying causes, both type 1 and type 2 diabetes exhibit similar stress-induced biochemical alterations, suggesting the presence of common molecular mechanisms responsible for diabetes-related tissue damage.{10}

A clear understanding of the biochemical alterations and stress-mediated pathways involved in diabetes mellitus is therefore critical for early diagnosis, effective therapeutic targeting, and prevention of chronic complications. Comprehensive evaluation of these interconnected mechanisms enhances insight into disease pathogenesis and supports the development of advanced strategies aimed at reducing oxidative stress, improving metabolic regulation, and strengthening overall diabetes management.

Epidemiology:

Diabetes mellitus (DM) has emerged as a rapidly expanding global public health challenge and is now widely understood to be more than a disorder of glucose regulation alone. It is increasingly characterised as a condition involving persistent biochemical and metabolic stress.{11} Current global estimates indicate that over 537 million adults are living with diabetes worldwide, with projections suggesting an increase to 643 million by 2030 and approximately 783 million by 2045.{12} This sharp rise in prevalence has resulted in a growing number of individuals experiencing prolonged oxidative stress, chronic inflammation, and metabolic disturbances associated with the disease.

Epidemiological evidence consistently shows that people with diabetes have markedly higher levels of biochemical stress markers, including enhanced oxidative stress, increased lipid peroxidation, excessive protein glycation, and compromised antioxidant defense mechanisms, when compared to non-diabetic individuals.{13} Such stress-related biochemical abnormalities have been documented across various populations and regions globally, indicating that metabolic stress is a common pathological feature of diabetes regardless of ethnic background or socioeconomic conditions.{14}

The worldwide increase in type 2 diabetes, largely attributed to sedentary behaviour, unhealthy dietary habits, rising obesity rates, population ageing, and rapid urbanisation, has further amplified the burden of stress-related metabolic disturbances.{15} Findings from large-scale population studies reveal a strong relationship between inadequate glycaemic control and elevated levels of circulating stress biomarkers, including malondialdehyde (MDA), C-reactive protein (CRP), and advanced glycation end products (AGEs). These observations suggest a dose-dependent association between chronic hyperglycaemia and the magnitude of biochemical stress.{16}{17}

In low- and middle-income countries, where diabetes prevalence is increasing most rapidly, delayed diagnosis and restricted access to preventive and therapeutic healthcare services often result in extended periods of poor glycaemic control and persistent biochemical stress.{18} Sustained exposure to these conditions heightens susceptibility to oxidative damage and accelerates the development of diabetes-related complications. Epidemiological studies indicate that individuals with long-duration or poorly managed diabetes are significantly more likely to present elevated oxidative and inflammatory markers,

which are closely linked to an increased risk of both microvascular and macrovascular complications.{19}

Moreover, despite differences in underlying pathophysiology, both type 1 and type 2 diabetes display comparable epidemiological patterns of oxidative and biochemical stress.{20} Population-based research suggests that these stress-associated biochemical alterations occur early in the disease process, often before the appearance of clinically detectable complications. This underscores the critical importance of early metabolic regulation and stress-mitigation strategies in diabetes management.{21} Collectively, these epidemiological observations highlight the extensive prevalence and public health relevance of biochemical stress in diabetes mellitus and emphasise the need for early diagnosis, preventive measures, and comprehensive disease-management approaches.

Pathophysiology:

Diabetes mellitus is primarily defined by persistent hyperglycaemia, which triggers a series of biochemical alterations that culminate in prolonged metabolic and oxidative stress. Elevated intracellular glucose levels stimulate alternative metabolic routes, including the polyol pathway, the hexosamine biosynthetic pathway, protein kinase C (PKC) activation, and increased generation of advanced glycation end products (AGEs).{22} Collectively, these mechanisms enhance the production of reactive oxygen species (ROS), exceed the capacity of endogenous antioxidant defence, and promote widespread cellular dysfunction in multiple tissues.{23}

Oxidative stress serves as a key pathogenic link between chronic hyperglycaemia and the development of diabetic complications. Excessive ROS formation leads to lipid peroxidation, oxidative modification of proteins, and DNA damage, thereby disrupting membrane stability, enzymatic activity, and mitochondrial integrity.{24} Concurrently, sustained hyperglycaemia suppresses the activity of essential antioxidant enzymes, including superoxide dismutase, catalase, and glutathione peroxidase, which further intensifies oxidative injury.{25} Mitochondrial dysfunction, driven by heightened electron transport chain activity, contributes to a self-perpetuating cycle of ROS overproduction and progressive cellular damage.{26}

Advanced glycation end products play a pivotal role in mediating biochemical stress in diabetes. AGEs modify the structure and function of proteins and interact with their specific receptor (RAGE), leading to activation of downstream inflammatory signalling pathways such as nuclear factor-κB (NF-κB).{27} This process induces the release of pro-inflammatory cytokines, including tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β), thereby sustaining chronic low-grade inflammation and oxidative stress.{28}

Neuroendocrine stress responses further exacerbate metabolic imbalance in diabetes. Continuous stimulation of the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system increases circulating levels of cortisol, catecholamines, and glucagon, hormones that counteract insulin action and aggravate insulin resistance.{29} These hormonal alterations enhance gluconeogenesis,

lipolysis, and proteolysis, resulting in dyslipidaemia, elevated free fatty acid flux, and increased lipotoxic stress.{30}

At the cellular level, prolonged exposure to glucotoxicity and lipotoxicity leads to pancreatic β-cell dysfunction and apoptosis through mechanisms involving endoplasmic reticulum stress, disrupted calcium homeostasis, and mitochondrial damage.{31} These changes diminish insulin secretory capacity and intensify glycaemic instability, reinforcing the cycle of biochemical stress. Over time, persistent oxidative and inflammatory stress promotes endothelial dysfunction, microvascular damage, and tissue fibrosis, forming the pathological basis of diabetic complications such as nephropathy, neuropathy, retinopathy, and cardiovascular disease.{32}

Overall, diabetes-related biochemical stress arises from a complex interaction between hyperglycaemia, oxidative injury, inflammatory processes, neuroendocrine imbalance, and disrupted cellular energy metabolism. Elucidating these interconnected pathways is crucial for identifying effective therapeutic targets aimed at alleviating metabolic stress, preserving cellular integrity, and preventing the progression of long-term diabetic complications.{33}

Clinical Characterization:

The clinical presentation of diabetes mellitus extends far beyond elevated blood glucose levels and is increasingly understood as a condition marked by persistent biochemical and metabolic stress, often emerging before the appearance of clinically apparent complications.{34} In a substantial proportion of individuals, particularly during the early phases of the disease, biochemical disturbances such as oxidative stress, chronic low-grade inflammation, and hormonal imbalance may remain asymptomatic, resulting in delayed detection and postponed therapeutic intervention.{35} These underlying subclinical abnormalities contribute to gradual tissue injury even in the absence of noticeable clinical signs.

From a clinical standpoint, biochemical stress in diabetes is characterised by sustained elevations in circulating glucose, free fatty acids, and stress-associated hormones, along with identifiable alterations in oxidative and inflammatory markers. Increased concentrations of malondialdehyde (MDA), advanced glycation end products (AGEs), and protein carbonyls are frequently reported, together with a decline in overall antioxidant capacity, including reduced glutathione levels and diminished activity of antioxidant enzymes such as superoxide dismutase and catalase.{36}{37} These biochemical changes demonstrate a strong association with longer disease duration and inadequate glycaemic control.

Chronic systemic inflammation represents another key clinical component of diabetes-related stress. Raised serum levels of inflammatory mediators, including C-reactive protein (CRP), interleukin-6 (IL-6), and tumour necrosis factor-α (TNF-α), are commonly observed and are closely linked to increasing insulin resistance and the progression of diabetes-associated complications.{38} Concurrently, heightened activation of the hypothalamic–pituitary–adrenal (HPA) axis results in elevated cortisol secretion, which further worsens hyperglycaemia, encourages central fat accumulation, and amplifies overall metabolic stress.{39}

In clinical practice, assessment of biochemical stress in diabetes involves a combination of conventional and advanced diagnostic tools. Standard glycaemic measures, including fasting plasma glucose and glycated haemoglobin (HbA1c), offer indirect indicators of sustained metabolic stress, while lipid profiling assists in identifying stress-related dyslipidaemia.{40} Increasingly, clinical evaluation incorporates markers of oxidative stress, inflammatory cytokines, and AGE-related parameters to identify patients at greater risk of tissue damage and future complications.{41}

Notably, despite differences in underlying pathophysiology, both type 1 and type 2 diabetes exhibit comparable clinical patterns of oxidative and inflammatory stress.{42} The extent of biochemical stress is strongly associated with the development of both microvascular and macrovascular complications, highlighting its significant clinical implications.{43} Recognition and evaluation of these biochemical and stress-related abnormalities within routine clinical care are therefore essential for comprehensive diabetes management and for informing targeted therapeutic approaches aimed at minimising oxidative injury and enhancing metabolic control.{44}

Biochemical Changes Stress Associated with Diabetes Mellitus:

Diabetes mellitus is marked by persistent metabolic dysregulation that generates extensive biochemical stress at systemic, cellular, and molecular levels. Chronic hyperglycaemia acts as the principal initiating factor, driving excessive glucose flow through non-physiological metabolic pathways and disrupting normal cellular equilibrium.{45} These biochemical abnormalities frequently arise early in the disease process and progressively worsen in the presence of inadequate glycaemic control.

A major biochemical alteration observed in diabetes is increased oxidative stress. Elevated intracellular glucose levels stimulate excessive generation of reactive oxygen species (ROS), largely due to dysfunction of the mitochondrial electron transport chain. The resulting ROS surplus exceeds the capacity of endogenous antioxidant defense mechanisms, leading to lipid peroxidation, oxidative modification of proteins, and DNA damage.{46} Concurrent reductions in the activity of antioxidant enzymes, including superoxide dismutase, catalase, and glutathione peroxidase, further intensify oxidative injury and perpetuate cellular stress.{47}

The formation and accumulation of advanced glycation end products (AGEs) constitute another critical feature of diabetes-associated biochemical stress. Persistent hyperglycaemia promotes non-enzymatic glycation of proteins, lipids, and nucleic acids, resulting in structural and functional alterations.{48} AGE accumulation disrupts intracellular signaling pathways, impairs enzymatic function, and induces cross-linking of extracellular matrix components. Engagement of AGEs with their receptor (RAGE) activates pro-inflammatory transcription factors such as nuclear factor-κB (NF-κB), thereby amplifying oxidative stress and inflammatory responses.{49}

Significant disturbances in lipid metabolism further contribute to metabolic stress in diabetes. Insulin resistance enhances lipolytic activity, leading to elevated circulating free fatty acids that accumulate in non-adipose tissues, including the liver, skeletal muscle, and pancreatic β-cells.{50} This ectopic lipid

deposition interferes with insulin signaling, promotes mitochondrial dysfunction, and triggers apoptotic pathways through endoplasmic reticulum stress and oxidative mechanisms.{51}

At the hormonal and neuroendocrine level, diabetes represents a chronic stress condition characterised by prolonged activation of the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system. Sustained elevations in cortisol and catecholamines oppose insulin action, stimulate gluconeogenesis, and contribute to increased glycaemic variability.{52} These stress-mediated hormonal alterations further exacerbate metabolic imbalance and promote long-term tissue damage.

Inflammatory processes are closely intertwined with biochemical stress in diabetes. Elevated circulating concentrations of inflammatory markers, including C-reactive protein (CRP), interleukin-6 (IL-6), and tumour necrosis factor-α (TNF-α), indicate the presence of chronic low-grade inflammation and correlate with disease severity.{53} Inflammatory signaling pathways impair insulin sensitivity, damage vascular endothelium, and accelerate the progression of diabetes-related complications.{54}

Together, these interrelated biochemical disturbances—encompassing oxidative stress, protein glycation, lipotoxicity, neuroendocrine imbalance, and chronic inflammation—establish a self-sustaining cycle of metabolic stress in diabetes mellitus. Over time, this prolonged biochemical burden results in cellular dysfunction, tissue remodelling, and the development of both microvascular and macrovascular complications.{55} Early recognition and targeted modulation of these stress-associated biochemical pathways are therefore essential for effective diabetes management and for preventing long-term adverse outcomes.{56}

Influence of Biochemical Changes on Diabetes Mellitus:

Persistent biochemical disturbances play a pivotal role in the onset, progression, and clinical severity of diabetes mellitus. Chronic hyperglycaemia combined with insulin resistance creates prolonged metabolic stress that disrupts intracellular signalling pathways, reduces glucose utilization, and alters energy balance in insulin-sensitive tissues such as skeletal muscle, liver, and adipose tissue.{57} Over time, these biochemical abnormalities progressively impair insulin sensitivity and contribute to the advancement of the disease.

Oxidative stress is a major determinant of diabetes pathophysiology. Elevated glucose availability enhances mitochondrial production of reactive oxygen species (ROS), resulting in oxidative modification of proteins, lipids, and nucleic acids.{58} This oxidative environment disrupts insulin signalling by impairing insulin receptor substrate (IRS) function and inhibiting downstream phosphatidylinositol-3-kinase (PI3K) pathways, thereby exacerbating insulin resistance and destabilizing glycaemic control.{59}

Advanced glycation end products (AGEs) further aggravate biochemical stress in diabetes. Accumulation of AGEs modifies protein conformation and enzymatic activity, interferes with cellular repair processes, and disturbs normal metabolic regulation.{60} Binding of AGEs to their receptor (RAGE) triggers

inflammatory signalling cascades, elevates cytokine production, and enhances oxidative stress, establishing a self-perpetuating cycle that worsens hyperglycaemia and metabolic dysfunction.{61}

Lipotoxic stress constitutes another critical biochemical contributor to diabetes progression. Insulin resistance promotes increased lipolysis in adipose tissue, leading to elevated circulating free fatty acids that accumulate in pancreatic β-cells and peripheral tissues.{62} Prolonged lipid overload induces endoplasmic reticulum stress, mitochondrial impairment, and β-cell apoptosis, ultimately reducing insulin secretory capacity and accelerating loss of glycaemic regulation.{63}

Neuroendocrine stress mechanisms also play a significant role in disease exacerbation. Sustained activation of the hypothalamic–pituitary–adrenal (HPA) axis increases circulating levels of cortisol and catecholamines, which oppose insulin action, stimulate hepatic gluconeogenesis, and raise blood glucose levels.{64} These hormonal responses intensify metabolic stress and further compromise glucose homeostasis.

Together, these interconnected biochemical processes—including oxidative stress, protein glycation, lipotoxicity, inflammation, and hormonal imbalance—profoundly influence the development and progression of diabetes mellitus. When left unmanaged, they accelerate pancreatic β-cell dysfunction, worsen insulin resistance, and promote the emergence of long-term complications. Addressing these biochemical pathways alongside effective glycaemic control is therefore essential for slowing disease progression, enhancing metabolic stability, and reducing the overall burden of diabetes.{65}

Neurohormonal and Metabolic Effect on Diabetes Mellitus associated with Stress:

Neurohormonal imbalance constitutes a vital mechanistic link between metabolic stress and the progression of diabetes mellitus. Chronic hyperglycaemia and insulin resistance lead to persistent activation of stress-regulatory systems, particularly the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system (SNS), resulting in marked hormonal and metabolic disturbances.{66,67} Continuous stimulation of these pathways elevates circulating levels of cortisol, catecholamines, glucagon, and growth hormone, all of which oppose insulin action and contribute to sustained hyperglycaemia.{68}

Enhanced sympathetic nervous system activity is commonly observed in individuals with inadequately controlled diabetes and is closely associated with heightened metabolic stress.{69,70} Increased plasma concentrations of norepinephrine and epinephrine impair insulin-stimulated glucose uptake in skeletal muscle, promote hepatic gluconeogenesis, and stimulate adipose tissue lipolysis, thereby increasing circulating free fatty acid levels.{71} This adverse neurohormonal environment worsens insulin resistance and establishes a self-reinforcing cycle in which metabolic stress drives further neurohormonal activation.{72}

Activation of the HPA axis plays an equally important role in stress-related metabolic deterioration. Prolonged cortisol excess enhances hepatic glucose output, suppresses peripheral glucose utilisation, and promotes accumulation of visceral adipose tissue.{73} Elevated cortisol levels are consistently linked

with poor glycaemic control, dyslipidaemia, and an increased inflammatory burden in individuals with diabetes.{74} Long-term exposure to glucocorticoids also contributes to pancreatic β-cell dysfunction and diminished insulin secretion, further destabilising glucose regulation.{75}

Metabolic stress is additionally intensified through disruptions in lipid and protein metabolism. Catecholamine-induced lipolysis increases free fatty acid availability, resulting in ectopic lipid deposition within the liver, skeletal muscle, and pancreatic β-cells.{76} This lipotoxic state induces mitochondrial impairment, oxidative stress, and endoplasmic reticulum stress, all of which interfere with insulin signalling and accelerate β-cell apoptosis.{77} Simultaneously, enhanced proteolytic activity contributes to loss of muscle mass and reduced metabolic adaptability, particularly in individuals with long-standing diabetes.{78}

At the molecular level, neurohormonal stress activates oxidative and inflammatory signalling pathways. Elevated catecholamine and cortisol levels stimulate reactive oxygen species generation and activate transcription factors such as nuclear factor-κB (NF-κB), leading to increased production of pro-inflammatory cytokines including tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6).{79} These inflammatory mediators directly impair insulin receptor signalling and promote systemic insulin resistance.{80}

Importantly, both clinical and experimental evidence demonstrate that effective glycaemic control, stress management, and targeted modulation of neurohormonal activity can mitigate these detrimental metabolic effects.{81} Therapeutic approaches aimed at enhancing insulin sensitivity, limiting excessive neurohormonal activation, and reducing oxidative and inflammatory stress are therefore essential components of comprehensive diabetes care. A deeper understanding of the complex interplay between neurohormonal activation and metabolic stress provides valuable insight into the pathophysiology of diabetes mellitus and identifies potential therapeutic targets for slowing disease progression and reducing associated complications.{82}

Additional Factors That Influence the Biological Changes on Diabetes Mellitus:

In addition to neurohormonal activation and metabolic stress, a variety of humoral, paracrine, and molecular mediators play critical roles in modulating the biological and pathophysiological alterations associated with diabetes mellitus. These mediators collectively intensify oxidative stress, inflammation, endothelial dysfunction, and tissue remodeling, thereby accelerating the development of diabetic complications.{83}

Endothelins, especially endothelin-1 (ET-1), are potent vasoconstrictive peptides that are elevated in individuals with diabetes. ET-1 increases vascular tone, promotes smooth muscle cell hypertrophy, stimulates fibroblast proliferation, and contributes to myocardial fibrosis, all of which accelerate structural and functional changes in the vasculature and heart.{84}

Pro-inflammatory cytokines, including tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), are consistently increased in diabetes. These cytokines drive chronic low-grade inflammation, activate

fibroblasts, disrupt extracellular matrix turnover, and induce cardiomyocyte apoptosis, ultimately leading to interstitial fibrosis and progressive impairment of cardiac function.{85}

Nitric oxide (NO) bioavailability is markedly reduced in the diabetic state as a consequence of endothelial dysfunction and uncoupling of endothelial nitric oxide synthase (eNOS). Diminished NO levels impair vasodilation, promote platelet aggregation, enhance vascular inflammation, and accelerate atherogenic processes, thereby increasing cardiovascular risk and contributing to pathological remodelling of the myocardium.{86}

Oxidative stress remains a central mechanism linking hyperglycaemia to tissue injury. Excess reactive oxygen species (ROS) disrupt mitochondrial function, activate pro-fibrotic signalling pathways, induce lipid peroxidation, and trigger apoptosis and necrosis in cardiomyocytes. ROS further amplify inflammatory responses and reduce NO bioavailability, establishing a self-reinforcing cycle that exacerbates structural and functional deterioration in the heart and vasculature.{87}

These mediators function within an integrated network rather than independently. For example, oxidative stress promotes cytokine production and lowers NO levels, while ET-1 signalling enhances ROS generation and inflammatory activity. This interconnected network of humoral and molecular mediators illustrates the complexity of biological alterations in diabetes mellitus and emphasizes the necessity of therapeutic strategies that target oxidative stress, inflammation, and endothelial dysfunction in conjunction with glycaemic control.{88}

The Main Components of Biochemicals associated with Diabetes Mellitus:

Diabetes mellitus involves a multifaceted biochemical environment that develops due to sustained hyperglycaemia, insulin resistance, and widespread metabolic disturbances. These biochemical alterations interact across systemic, cellular, and molecular levels, leading to progressive tissue damage, organ dysfunction, and long-term complications. Key contributors to this process include disruptions in glucose and lipid metabolism, oxidative balance, inflammatory signalling, and hormonal regulation, all of which collectively drive disease progression. {89}

Hyperglycaemia and Advanced Glycation End Products (AGEs):

Persistent elevation of blood glucose is the fundamental biochemical abnormality in diabetes and serves as the initiating factor for several pathogenic mechanisms. Excess glucose participates in non-enzymatic glycation reactions with proteins, lipids, and nucleic acids, resulting in the formation of advanced glycation end products (AGEs). The accumulation of AGEs modifies protein structure, impairs normal biological function, increases tissue rigidity, and interferes with intracellular signalling pathways. Interaction of AGEs with their specific receptors (RAGE) triggers pro-inflammatory and oxidative signalling cascades, thereby accelerating vascular injury and contributing to organ dysfunction. {90}

Dyslipidaemia and Lipotoxicity:

Disturbances in lipid metabolism represent a prominent biochemical feature of diabetes mellitus. Increased levels of circulating free fatty acids, triglycerides, and altered lipoprotein composition lead to lipid accumulation in non-adipose tissues such as the heart and vascular system. This lipotoxic environment disrupts mitochondrial activity, enhances oxidative stress, and induces programmed cell death in cardiomyocytes and endothelial cells. Such biochemical alterations significantly contribute to insulin resistance and the development of diabetes-related complications. {91}

Oxidative Stress and Reactive Oxygen Species (ROS):

Oxidative stress plays a central role in the biochemical pathology of diabetes, arising from an imbalance between reactive oxygen species production and antioxidant defence mechanisms. Hyperglycaemia stimulates excessive ROS generation through mitochondrial dysfunction and activation of enzymes such as NADPH oxidase. Elevated ROS levels damage cellular lipids, proteins, and DNA, impair nitric oxide signalling, and intensify inflammatory processes. As a result, oxidative stress acts as a key link between hyperglycaemia, endothelial dysfunction, fibrosis, and cellular injury. {92}

Inflammatory Mediators and Cytokines:

Diabetes mellitus is increasingly characterized as a chronic low-grade inflammatory condition. Increased circulating concentrations of inflammatory cytokines, including TNF-α, IL-6, and IL-1β, interfere with insulin signalling pathways, impair endothelial function, and promote fibrotic tissue remodelling. These inflammatory mediators also interact closely with oxidative stress pathways, creating a persistent inflammatory state that accelerates tissue injury and disease progression. {93}

Hormonal and Neurohormonal Biochemical Changes:

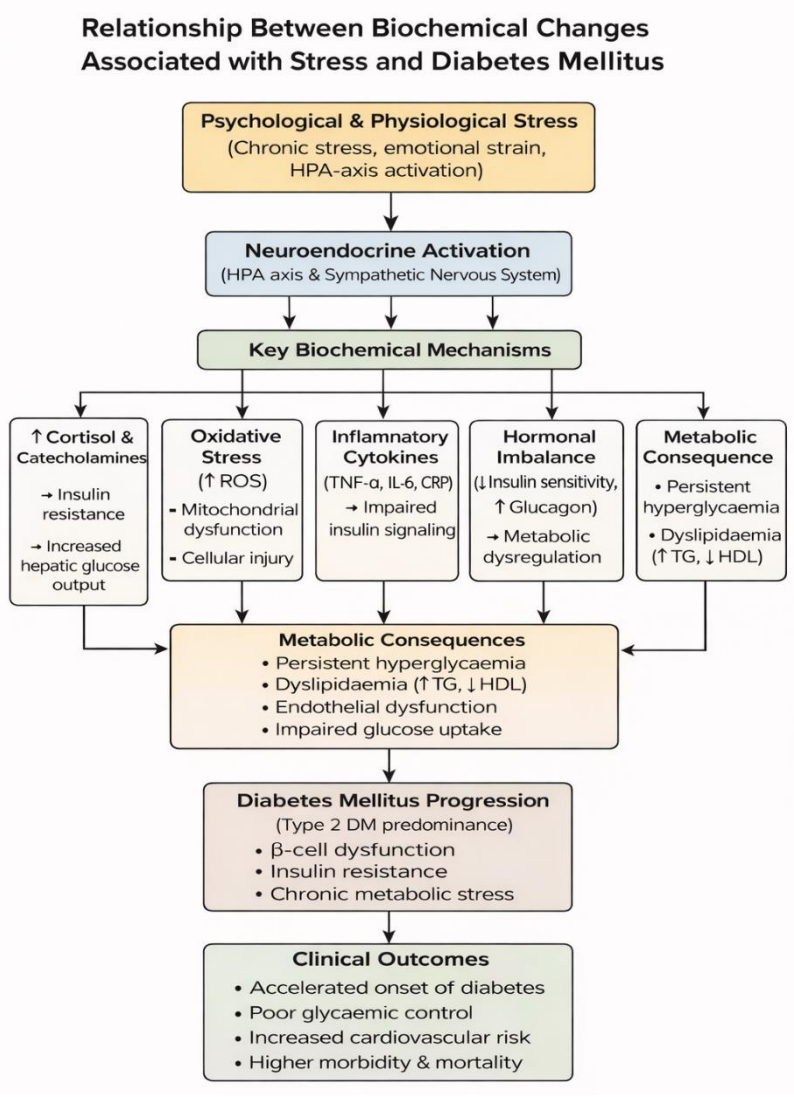
Insulin resistance or deficiency in diabetes is accompanied by dysregulation of counter-regulatory hormones such as glucagon, cortisol, catecholamines, and components of the renin–angiotensin–aldosterone system. These hormonal disturbances further aggravate hyperglycaemia, stimulate excessive lipolysis, and contribute to sodium retention and vascular dysfunction. Heightened neurohormonal activity additionally promotes oxidative stress, inflammation, and structural remodelling within target organs. {94}

Altered Nitric Oxide and Endothelial Biochemistry:

Diabetes is associated with a significant reduction in endothelial nitric oxide bioavailability due to increased oxidative degradation and impaired activity of endothelial nitric oxide synthase. This biochemical impairment leads to reduced vasodilatory responses, increased platelet aggregation, and enhanced vascular inflammation. Consequently, diminished nitric oxide signalling plays a crucial role in the development of atherosclerosis and microvascular complications. {95}

Overall, these biochemical mechanisms operate in a highly interconnected manner rather than independently. Hyperglycaemia-induced AGE formation intensifies oxidative stress and inflammation, dyslipidaemia exacerbates mitochondrial dysfunction, and hormonal imbalances sustain metabolic derangements. Together, this complex biochemical network underlies the systemic nature of diabetes mellitus and drives the progression of its cardiovascular and metabolic complications. {96}

Relationship Between Biochemical Changes associated with Stress and Diabetes Mellitus:



(Source: From References 97-99)

Management Therapeutic Approach in Biochemical Changes associated with Stress in Diabetes Mellitus:

Persistent psychological and physiological stress contributes substantially to both the development and progression of diabetes mellitus by intensifying biochemical abnormalities such as hyperglycaemia, insulin resistance, oxidative imbalance, inflammation, and neurohormonal dysfunction. Effective diabetes management therefore requires therapeutic approaches that extend beyond glycaemic regulation and specifically address stress-related biochemical pathways in order to prevent metabolic deterioration and long-term complications.

Pharmacological modulation of glucose metabolism remains a primary strategy for minimizing stress-induced biochemical damage. Maintaining optimal glycaemic control reduces glucotoxic effects, limits oxidative stress, and suppresses stress-mediated activation of inflammatory and neuroendocrine pathways.{100} Metformin, the first-line treatment for type 2 diabetes, enhances insulin sensitivity and suppresses hepatic gluconeogenesis. In addition, it has been shown to influence stress-related metabolic responses by reducing circulating cortisol concentrations and pro-inflammatory markers.{101}

Recent advances in glucose-lowering therapies offer additional advantages by targeting biochemical mechanisms associated with chronic stress. Sodium–glucose co-transporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists provide benefits beyond glycaemic control, including reductions in sympathetic nervous system activation, body weight, oxidative stress, and systemic inflammation. Clinical studies demonstrate that these agents decrease cardiovascular risk and enhance metabolic stability in individuals exposed to prolonged stress. {102,103} These effects are partly mediated through improvements in mitochondrial function, suppression of inflammatory cytokine release, and regulation of neurohormonal activity.{104}

Chronic stress-induced stimulation of the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic nervous system significantly exacerbates insulin resistance and metabolic dysregulation. As a result, non-pharmacological stress-management strategies play a vital role in comprehensive diabetes care. Evidence supports structured lifestyle interventions such as regular physical exercise, mindfulness-based stress practices, cognitive behavioural therapy, and adequate sleep in lowering cortisol levels, enhancing insulin sensitivity, and reducing inflammatory biomarkers among individuals with diabetes.{105}

Antioxidant and anti-inflammatory interventions further support metabolic control by counteracting stress-related biochemical injury. Diets enriched with antioxidants, including polyphenols, omega-3 fatty acids, and essential micronutrients, help mitigate oxidative damage and restore redox homeostasis.{106} In selected clinical contexts, pharmacological agents targeting oxidative stress and inflammatory pathways may provide additional protection by limiting biochemical damage to pancreatic β-cells and insulin-responsive tissues.{107}

In conclusion, optimal diabetes management requires an integrated therapeutic framework that addresses both metabolic abnormalities and stress-related biochemical disturbances. Early diagnosis, personalized

pharmacological treatment, lifestyle modification, and psychological stress management collectively reduce biochemical burden, improve glycaemic stability, and decrease the risk of long-term cardiovascular and metabolic complications associated with diabetes mellitus.{108}

Conclusion:

Biochemical changes arising from prolonged psychological and physiological stress play a crucial role in the development, progression, and complication spectrum of diabetes mellitus. Continuous stimulation of stress-response systems, particularly the hypothalamic–pituitary–adrenal axis and the sympathetic nervous system, intensifies hyperglycaemia, insulin resistance, oxidative imbalance, inflammatory activity, and neurohormonal dysregulation. These processes collectively accelerate metabolic decline and promote damage to target organs. {108} Such stress-mediated biochemical disruptions not only impair glycaemic regulation but also significantly increase the risk of cardiovascular, renal, and microvascular complications frequently observed in individuals with diabetes. {109}

Management of stress-related biochemical alterations in diabetes therefore necessitates a comprehensive therapeutic approach that goes beyond glycaemic control alone. Strategies combining optimal glucose regulation, pharmacological agents with anti-inflammatory and antioxidant effects, regulation of neurohormonal pathways, and structured lifestyle-based stress management provide meaningful improvements in metabolic stability and long-term clinical outcomes. {110} Growing evidence underscores stress as a modifiable risk factor, with interventions such as regular physical exercise, behavioural therapies, and mindfulness-based practices demonstrating favourable effects on cortisol modulation, inflammatory biomarker reduction, and enhanced insulin sensitivity. {111}

As insights into the biochemical interactions between stress and diabetes continue to advance, future research is likely to facilitate the development of more precise therapeutic interventions targeting specific molecular pathways. Early recognition of stress-induced biochemical dysregulation, combined with timely multidisciplinary management, holds considerable promise in reducing disease burden, improving quality of life, and limiting the overall impact of diabetes mellitus and its related complications. {112}

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