ORIGINAL ARTICLE

Altered Glucose Metabolism and Acute Vascular Events

Gundu H. R. Rao

Emeritus Professor, Laboratory Medicine and Pathology Director, Thrombosis Research, Lillehei Heart Institute, University of Minnesota, Minneapolis, Minnesota, USA

ABSTRACT

Diabetes Mellitus is a major risk factor for the development of cardiovascular disease (CVD) and contributes significantly to morbidity and mortality related to CVDs. American Heart Association (AHA) considers diabetes, to be one of the 7 major controllable risk factors, responsible for the progress of cardiovascular disease. Acute vascular events are triggered by underlying mechanisms, which precipitate ischemia of the arteries, reduce the flow of blood, and create hypoxia, tissue damage, and eventual end organ failure. Metabolic risks such as oxidative stress, inflammation, insulin resistance, elevated blood glucose, vascular dysfunction, and vessel-wall atherosclerosis, promote the progress of the vascular disease. Chronic hyperglycemia has been shown to play a role in the initiation of these metabolic risks, and promote the development of arterial atherosclerosis, activation of blood platelets, and coagulation pathways. In this overview, we have described some of the ill effects of hyperglycemia and discussed few specific findings, which explain altered signaling events that promote the development of a prothrombotic state. According to a recent global survey, 43% with type-2 diabetics in North America have cardiovascular disease. Globally, there are more individuals with impaired glucose tolerance and prediabetic condition than diabetes. This 'at risk' group should be targeted for developing prevention strategies. We would like to see the development of a robust screening initiative at the population level, to identify the at-risk population, by monitoring the impaired glucose tolerance. Early detection of the altered glucose metabolism will provide an opportunity for public health experts, to develop appropriate prevention strategies.

Key words: Hyperglycemia, oxidative stress, endothelial dysfunction, arterial plaque, vascular events.

INTRODUCTION

Acute vascular events such as heart attacks and stroke have remained major killers of the century. Acute vascular events can occur in any regional vascular bed and introduce ischemia by preventing oxygen supply to the affected tissues. Prevalence of cardiovascular disease nearly doubled from 271 million in 1990 to 523 million in 2019, and the number of CVD deaths, steadily increased to 18.6 million in 2019 worldwide (1). Framingham heart (FH) studies initiated at the early part of this century, developed for the first-time, information on several modifiable risk factors that contributed to the development of heart disease. In brief, the Framingham Heart Study, funded by the National Institute of Health and managed by the Boston University, spans 3 generations of well phenotyped White persons, and

Address for correspondence:
Gundu H. R. Rao Emeritus Professor, Laboratory Medicine and Pathology Director, Thrombosis Research, Lillehei Heart Institute, University of Minnesota, Minneapolis, Minnesota, USA.

DOI: 10.33309/2639-8265.040104

2 cohorts composed of racial and minority groups (1) Based on this epidemiology study, researchers developed risk factor assessment strategies, and a ten-year risk assessment algorithm, for the prediction of heart disease (2). Much of our appreciation of the pathophysiology of heart disease comes from the results of FH studies. These studies established that the atherosclerosis is an arterial abnormality, and the traditional risk factors, such as high blood pressure, high blood cholesterol, diabetes, and cigarette smoking, promote the development of coronary artery disease (3). Several studies have demonstrated that robust management of modifiable risk factors, and promotion of a heart healthy lifestyle, significantly reduces premature mortality to due to CVDs (4-6).

Epidemiology researchers from the Imperial College, London, estimated the potential role of trend in population body mass index (BMI), systolic blood pressure, serum cholesterol (LDL-C), and smoking, in cardiometabolic mortality in 26 industrialized countries. They found, age-standardized cardiometabolic mortality declined in all 26 countries studied. In the 80s, the MONICA (multinational MONItoring of trend and determinants in CArdiovasculardisease) project was established, to examine the relationship between risk factor changes in population trends over a 10-year period, using data from 38 centers in 21 countries. In this project, changes in smoking, blood pressure, serum cholesterol, and body mass index explained the cross-population variation in CVD decline (7). Despite the decline in CVD mortality observed in these and other studies, it is apparent that the death due to heart attack and stroke remain very high. The million-dollar question then is, -are there other risk factors, which contribute to the excess CVD death? Indeed, the Framingham risk assessment calculator does not even include any risk assessment for the possible role played by the two major contributors, -blood platelets and coagulation pathways. In this overview, we will briefly discuss some of the other lesser-known risk factors, which may contribute to the progress of the vessel-wall disease and the precipitation of acute vascular events.

OXIDATIVE STRESS AND DIABETIC COMPLICATIONS

Altered glucose metabolism in diabetics, plays an important role in the development of diabetes mediated clinical complications, both microvascular and cardiovascular. The metabolic abnormalities induce mitochondrial superoxide production in endothelial cells of both large and small vessels. This enhanced superoxide production causes activation of different pathways, leading to pathogenesis of clinical complications such as, polyol pathway, increased formation of advanced glycation end products (AGEs), activation of protein kinase C isoforms, and increased activity of hexosamine pathway (9). Furthermore, it also inactivates two critical vasodilatory, anti-atherosclerotic enzymes, endothelial nitric oxide (NO) synthase and prostacyclin synthase. Insulin resistance which is a major contributor for the observed hyperglycemic state in the diabetics also increases mitochondrial Reactive Oxygen Species (ROS) from free fatty acids. ROS directly increases expression of inflammatory and adhesion factors, formation of oxidized -low density lipoproteins and insulin resistance (9). Overexpression of superoxide dismutase seems to prevent diabetes-related clinical complications such as diabetic retinopathy, nephropathy, and cardiomyopathy suggesting a role for ROS in these observed clinical complications.

Oxidative stress is considered as an imbalance between pro- and antioxidant species. Excess of free radical, peroxynitrile and ROS cause lipid peroxidation, thus damaging cell membranes and lipoproteins. They also inhibit vasodilatory prostanoids and deplete cellular glutathione. Studies from our laboratory at the University of Minnesota, demonstrated the role of glutathione in platelet function and reported platelet hypersensitivity induced by 1-chloro-2, 4 dinitrobenzene, lipid hydroperoxides, inhibitors of lipoxygenase and glutathione depleting agents (10). They further demonstrated that the glutathione deficient platelets, upon stimulation by arachidonic acid produce increased quantities of proaggregatory thromboxane, and are hyperactive (11, 12). Our studies also demonstrated a circadian rhythm in platelet glutathione levels (13) these studies on the role of glutathione in inducing platelet dysfunction demonstrate, that lower antioxidant status in platelets, predisposes them to hypersensitivity to the action of arachidonic acid, promotes generation of increased quantities of PG endoperoxides and initiates a prothrombotic condition. Nuclear factor erythroid 2-related factor 2 (Nrf2)-binding protein attached to the cytoskeleton seem to function as “oxidative stress sensor.” and seem to induce expression of an array of antioxidant response element genes, to regulate the pathophysiologic and physiological outcomes of oxidant exposure. Several compounds have been reported in recent years, as activators of this mechanism. Of these Protandim (Life Vantage Corp, Salt Lake City), sulforaphane, bardoxolone methyl and dimethyl fumarate have been shown to be safe and beneficial in human subjects (14).

ALTERED GLUCOSE METABOLISM OXIDATIVE STRESS AND SEVERITY OF CORONAVIRUS DISEASE

We have described in our earlier articles that the coronavirus severity is enhanced my comorbidities such as hypertension, excess weight, obesity, and type-2 diabetes (15). We also have described this virus disease is a 'disease of the blood vessels' in which severity of the disease results in vascular dysfunction and a prothrombotic condition. Several studies have shown that diabetes, especially hyperglycemia predicts worse outcomes in hospitalized patients (16). In a retrospective cohort study, Chinese researchers report that elevated blood glucose level was an independent risk factor to predict the progression to critical cases/death in hospitalized patients with COVID-19. Researchers from Baylor College of Medicine, USA reported that COVID-19 infection is associated with severe intracelluar glutathione (GSH) deficiency, elevated oxidative stress and oxidant damage. In their observations these defects were present in all age groups. Based on the results of their study they suggest glycine and N-Acetylcysteine (GlyNAC) supplementation for overcoming the GSH deficiency, lowering oxidative stress and oxidant damage (17). These observations further support the results of our earlier studies which demonstrated the role of hyperglycemia and oxidative stress, in altering arachidonic acid pathway to promote a pro-thrombotic state (10-13).

HYPERGLYCEMIA, INFLAMMATION, AND ENDOTHELIALDYSFUNCTION

Chronic hyperglycemia is a recognized causal factor in the pathogenesis of diabetes, progression of the disease and its clinical complications (18). Increased blood glucose over a period, induces large number of alterations in vascular tissue and potentially promotes atherosclerosis. Elevated glucose levels induce structural and functional changes in different proteins in the body including albumin, globulins, fibrinogen, and collagens. Glycation of these proteins is associated with initiation of deleterious changes in the function of the various organ systems. Some of the suggested altered states include 1) non-enzymatic glycosylation of proteins and lipids, 2) protein kinase C (PKC) activation, 3) increased flux through the hexosamine pathway, 4) increased oxidative stress and 5) Inflammation. Chronic effects of hyperglycemia are irreversible and lead to the development of progressive dysfunction of cells, tissues, and organs. Of the various mechanisms that are affected by hyperglycemia, one of the important mechanisms responsible for accelerated atherosclerosis in diabetics is the non-enzymatic reactions between proteins or lipoproteins in arterial walls. Some of the early glycosylation products of long-lived proteins, such as vessel wall collagen, continue to undergo complex reactions and end up as advanced glycosylation products (AGEs). These advanced glycosylation products interact with AGE binding proteins or receptors (RAGE). AGE-RAGE interaction mediates oxidative stress generation, promotes vascular inflammation, macrophage, and platelet activation, and facilitates migration of inflammatory cells to RAGE-rich areas of the vessel wall, and thus contributes to the pathogenesis of the vascular dysfunction.

Altered blood glucose levels seem to initiate inflammatory responses and promote phenotypic conversion of endothelial cells. Endothelial cells of microvasculature are both participants and regulators of inflammatory process. Activated endothelial cells are characterized by enhanced permeability, elevated leukocyte adhesion molecule expressions, recruitment of leukocytes, and reduced anti-thrombotic properties (19). Mediators of endothelial activation include several proinflammatory cytokines such as tumor necrosis factor, interleukin -1ß; bacterial lipopolysaccharide and vasoconstrictors (angiotensin-11, endothelin-1), neutrophil recruitment, shear forces, and extracellular matrix proteins, -fibronectin, and fibrinogen. Endothelial cell activation may progress by phases.First phase is independent of gene expression (type-1), and second phase is dependent on gene expression (type-11). Irrespective of the type of activation, these processes share some common features: an increased local blood flow, increased warmth of inflamed tissues, leakage of plasma-protein-rich fluid (exudate), swelling of the inflamed tissue, and recruitment of leukocytes.

The type one activation is mediated by ligands that bind to the extracellular domains of the heterotrimeric G-protein-coupled receptors. The GDP to GTP exchange facilitates dissociation of the G-protein alpha subunit from the G-proteinß, gamma, dimer, and activates membrane associated phospholipase C (PLC). This enzyme cleaves phosphatidyl inositol -4, 5 bisphosphate,

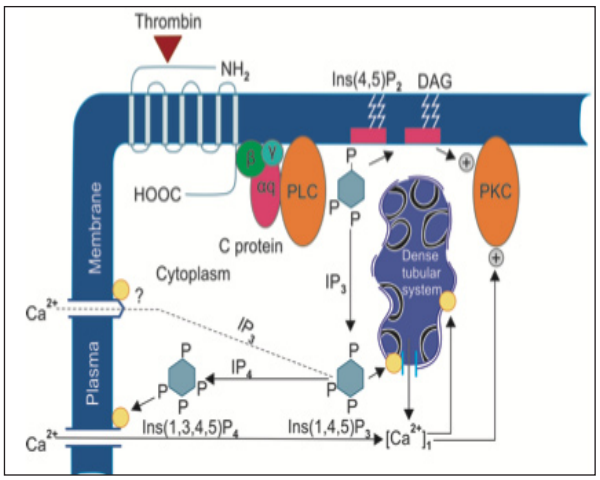

Figure 1. Signal Transduction and Phosphatidyl Inositol Metabolism

(Source: Personal collection)

Which results in the formation of inositol 1, 4, 5 -trisphosphate (IP3) and a diglyceride (DAG) (Fig 1). IP3modulates the cytosolic free calcium and increases the cellular calcium levels and activates phospholipase A2, resulting in the release arachidonic acid from the membrane associated phospholipids. Free arachidonic acid is converted by cyclooxygenases (COX) into Prostacyclin (PGI_2) which is a vasodilator. It is believed that inhibition of PGI_2-dependent vasodilation and increases in blood flow, may be the mechanism by which COX-inhibitors reduce inflammation. Elevated levels of calcium may also bind calmodulin and play a role in the activation of nitric-oxide (NO) synthase. Elevated calcium levels may also play an important role in leukocyte recruitment. Oxidative stress, inflammation, and hyperglycemia in concert, enhance endothelial dysfunction. It is well known that compromised endothelial function is observed in people with insulin resistance and metabolic syndrome, often preceding the onset of disease by several years. In individuals with metabolic syndrome, primary metabolic alteration is chronically elevated blood glucose, which is to a great extent followed by inflammation and oxidative stress. Constant exposure of vascular endothelium to hyperglycemia leads to a variety of events leading to altered signaling pathways, that negatively effect and compromise vascular function (20).

ALTERED GLUCOSE METABOLISM AND ITS EFFECT ON ARACHIDONIC ACID METABOLISM

The 1982 Nobel Prize in Physiology and Medicine was awarded to Sune Bergstrom and Bengt Samuelsson, both of Karolinska Research Institute, Stockholm, Sweden, and John Wane of Wellcome Research Foundation in Beckenham, England, for their research on chemical messengers called prostaglandins. In the early 80s, we at the University of Minnesota were also interested in the role of these chemical messengers in modulating thrombosis and hemostasis (21).

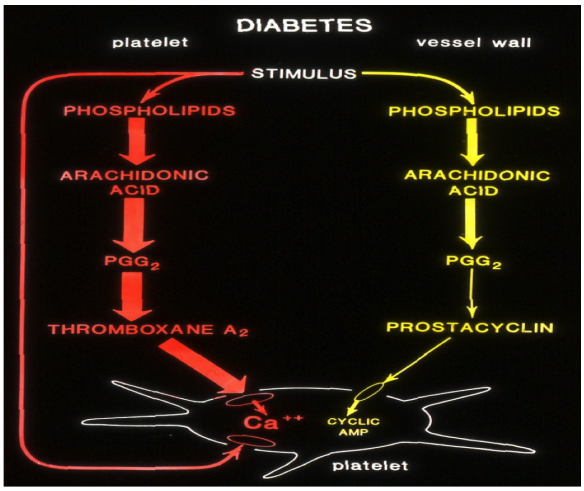

Figure 2. Arachidonic acid Conversion to Thromboxane A_2 and Prostacyclin I_2 in Diabetic Rat.

(Courtesy: Dr Jon Gerrard, Winnipeg, Manitoba, Canada)

In our exploratory studies, rats were rendered diabetic by injection of streptozotocin, and the ability of platelets and vessel-wall tissue to make prostanoids from the substrate arachidonic acid (AA), were compared with matched controls. We evaluated the incorporation, release, and conversion of radiolabeled AA, to thromboxane B_2 and 6- keto-$PGF_{1a,}$ -stable metabolites of respective active derivatives of AA. Conversion of arachidonic acid to proaggregatory thromboxanes was higher in the diabetic rats and conversion of AA to vasodilatory metabolite prostacyclin was less in the diabetic rats, suggesting a shift to prothrombotic state (Fig 2). The changes observed both in platelet and vascular metabolism of arachidonic acid were normalized by pancreatic islet tissue transplantation, suggesting a disease specific effect (effect of hyperglycemia). The results of these studies suggest a significant imbalance in thromboxane A_2 and PGI_2 production, in diabetic animals demonstrating the effect of hyperglycemic state on vascular dysfunction.

HYPERGLYCEMIA AND ATHEROSCLEROSIS

Chronic blood glucose elevation may accelerate formation of early-mid stage lesions of atherosclerosis, by promoting adhesion molecule expression in endothelial cells through

epigenetic changes, including activation of PKC, RAGE, and increased production of reactive oxygen species (ROS). Furthermore, insulin at high concentrations can accelerate the atherosclerosis process by multiple mechanisms, including lipogenesis leading to excess LDL synthesis. Early phases of initiation, progression, and development of atherosclerotic plaque are different from the formation of clinically significant vulnerable and stable plaques. Early-to-mid-stage atherogenesis involves accumulation and building up of lipoprotein B (apoB)-containing lipoproteins; activation of endothelial cells; recruitment of monocytes, leukocytes, and other inflammatory cells; cholesterol enrichment and migration of smooth muscle cells (22). Elevated levels of blood glucose increase intracellular oxidative stress in endothelial cells and upregulates Protein Kinase C (PKC) activity. This in turn promotes adhesion of recruited neutrophils to smooth muscle cells. Researchers at the Jefferson University School of Medicine, Philadelphia, have shown that inhibition of PKC activity ameliorates endothelial dysfunction in hyperglycemia by attenuating leukocyte-endothelium interactions *in vivo* via reduced oxidative stress (23).

MORPHOLOGY OF ATHEROSCLEROTIC PLAQUES AND ACUTE VASCULAR EVENTS

In the early phases of atherosclerotic plaque development, endothelial dysfunction seems to play an important role in initiating permeability of atherogenic lipid (LDL) particles, which leads to foam cell formation that contains a lipid core comprising of cholesterol. Lipid particles residing in the foam cells contribute to the inflammation of the endothelium (23). Three-dimensional carotid ultrasound imaging improves the visualization and quantification of carotid plaque volume and morphology, as well as monitoring progression of atherosclerosis and the benefits or otherwise of lipid lowering drugs. (24). Atherosclerosis is a systemic disease, characterized by plaques with retained lipids, inflammatory cells, apoptotic cells, calcium, and extracellular matrix proteins. Professor David Spence and associates from the Stroke Prevention and Atherosclerosis Research Centre, Roberts Research Institute, Western University, London, Canada, have demonstrated that lowering of the LDL-Cholesterol in the plaque and regression of the plaque volume is associated with lower cardiovascular risk (25, 26). Arterial inflammation is highly prevalent in middle-aged individuals, with known subclinical atherosclerosis. In a collaborative study by the US and Spanish researchers, arterial inflammation was reported in 48% of asymptomatic individuals and plaques in 90%. Plaque burden, defined as plaque presence, number and volume was significantly higher in individuals with arterial inflammation (27). Researchers of CANTOS Trial Group demonstrated that anti-inflammatory therapy targeting the interleukin-1β innate immunity pathway with canakinumab, a monoclonal antibody, at a dose of 150 mg every three months, led to a significantly lower rate of recurrent cardiovascular events than placebo, independent of lipid-level lowering, -suggesting for the first time, the role of inflammation in the precipitation of acute vascular events (28).

SGLT2 INHIBITORS OFFER CARDIO PROTECTION

Several recent studies have demonstrated that sodium-glucose cotransporter (SGLT2) inhibitors exert cardioprotective and renoprotective effects. In large-scale randomized controlled studies, SGLT2 inhibitors (Dapaglifozin, Canagliflozin, Empagliflozin, Ertugliflozin etc.,) have been shown to reduce the risk of hospitalization by 30% and decrease in the risk of cardiovascular death (29). Canadian researchers in a state-of-the-art review, contemplate on the possible mechanisms by which these inhibitors offer cardioprotection, which include: 1) blood pressure lowering; 2) increasing diuresis; 3) improving cardiac energy metabolism; 4) preventing inflammation; 5) facilitating weight loss; 6) improving glucose control; 7) inhibiting the sympathetic nervous system; 8) preventing adverse cardiac modeling; 9) preventing ischemia/perfusion injury; 10) inhibiting the cardiac Na+/H+ exchanger; 11) inhibiting SGLT2; 12) reducing hyperuricemia; 13) increasing autophagy and lysosomal degradation; 14) decreasing epicardial fat mass; increasing erythropoietin levels; 16) increasing circulating progenitor cells; 17) decreasing oxidative stress and 18) improving vascular function (30). Australian researchers in a drug-induced tandem stenosis mice model demonstrated, that the SGLT2 inhibitors stabilize diabetes-induced atherosclerotic plaque stability (31). In this study, diabetic mice showed an increase in the size of unstable atherosclerotic plaques as well as the plaque instability markers MCP-1, CD68, and necrotic core size. Mice treated with dapagliflozin (Farxiga) demonstrated attenuated glucose and triglyceride levels and demonstrated plaque stabilization with enhanced collagen accumulation, increased fibrosis, increased cap-to-lesion height ratios, and significant upregulation of the vasculo-protective NADPH oxidase expression.

DISCUSSION

Large scale clinical studies such as The Seven countries study, North Karelia study, MONICA study, INTERHEART study, and study of 26 Industrialized Nations have demonstrated, that modification of lifestyle and adhering to a healthy lifestyle, significantly reduces the premature death caused by cardiovascular disease (32-34, 4-7). Despite this observed decline in CVD-related deaths, the metabolic diseases such as hypertension, excess weight, and type-2 diabetes have increased rapidly in the last four decades to epidemic proportions (35). No country has reduced, reversed, or prevented the increase in the prevalence of these diseases. Diabetes is one of the top 10 causes of death globally; Individuals with diabetes have a 2-3 folds higher risk of all-cause mortality. Globally, the excess mortality attributable to diabetes in adults is estimated to be 3.8 million deaths. Nearly 50% of type-2 diabetes patients die prematurely of a CVD cause. By and large clinicians manage diabetic patients by treating the observed hyperglycemic condition. Robust management of blood glucose level, increase in physical activity, adhering to a heart healthy diet and healthy lifestyle, can indeed, keep a diabetic free of clinical complications for several decades. Having said that, we must warn the readers, that despite good management of the glycemic load, chronic glycemia exerts its ill effects on the physiology and function of all organ systems.

Metabolic risks such as, oxidative stress, inflammation, altered metabolism of carbohydrates and lipids, increased blood glucose, insulin resistance, endothelial dysfunction, subclinical atherosclerosis, excess weight, obesity, and type-2 diabetes, promote the development of vascular dysfunction leading to coronary artery and cerebral artery diseases. Of these various metabolic risks, endothelial dysfunction, development of atherosclerotic plaques, narrowing of the arteries, activation of blood platelet and coagulation pathways, play a critical role in the precipitation of acute vascular events. Prolonged elevation in blood glucose as well as bacterial and viral infection seem to initiate similar pathophysiological sequalae of events, such as oxidative stress, inflammation, vascular dysfunction, resulting in ischemia, tissue damage and ultimate end organ failure (36-40). In this short overview, we have described some of the mechanisms that are modulated by excess glucose, oxidative stress, inflammation and subclinical atherosclerosis, activation of the blood platelet and coagulation pathways, which lead to the development of prothrombotic state, readers are urged to refer to original articles and monographs for additional information.

By and large clinicians manage diabetes by recommending treatments that lower blood glucose. Some of these treatments have been shown to provide cardioprotection. Increase in insulin resistance, lipolysis and hepatic glucose production is characteristic features of type-2 diabetes. Dr. Gencer Sancar and associates from Gene Expression Laboratory, Salk Institute, La Jolla, California report, that fibroblast growth factor (FGF1) has robust antidiabetic effect and FGF1 and Insulin control lipolysis by convergent pathways (41). Results of these studies are encouraging, as they provide information about a new route for regulating blood glucose independent of insulin. Furthermore, we hope emerging discoveries on the role of miRNAs in the development of diabetes-related clinical complications; will provide us the needed knowledge, to develop appropriate interventional therapeutics.

Increase in metabolic diseases worldwide has created a huge population 'at risk' for the development of acute vascular events. Just management of the modifiable risk factors may not be sufficient for reduction or reversal in the increase of metabolic diseases. Jay Cohn, the director, Cardiovascular Disease Prevention Institute, University of Minnesota advocates the treatment of the disease itself, than focusing on the management of risk factors. This represents a paradigm shift away from identification of risk factors and their management, towards the treatment of early disease, to prevent further disease progression into cardiovascular morbid events (CMVEs). Professor Cohn's most recent work has focused on the predictive value of non-invasive tests utilized at the Rasmussen Center for Cardiovascular Disease Prevention, University of Minnesota (42). Professor Henry Blackburn, a pioneer cardiovascular epidemiologist at the University of Minnesota, concluded his article in my book on Coronary Artery Disease, with the following statement: "The ultimate public health goal is not just to control diseases or just reduce high risk, but to prevent high risk in the first place among individuals and entire populations (43). We the members of South Asian Society on Atherosclerosis and Thrombosis (www.sasat.org), appeal to the global public health experts, to recommend population level screening of 'at risk' patients for diabetes, by offering robust impaired glucose tolerance tests, as well as initiating appropriate interventions to reduce, or reverse impaired glucose metabolism.

CONCLUSION

Impaired glucose metabolism leads to hyperglycemia, a hallmark of diabetes. It is very well established that chronic elevated levels of blood glucose promote pathological changes leading to the development of risk factors such as oxidative stress, inflammation, altered blood flow, endothelial dysfunction and development of subclinical atherosclerosis. These factors alone, or collectively, do not trigger thrombotic episodes leading to acute vascular events. The major actors responsible for activating these acute events are development of vulnerable plaque, narrowing of the artery, and activation of blood platelets and coagulation pathways. We have discussed the role of elevated glucose in altering various signaling pathways to promote the development of thrombotic state. We also have discussed how the severity of coronavirus disease is enhanced by similar risk factors. Clinicians manage diabetics by recommending drugs that manage the blood glucose levels. Recent findings that some of these drugs offer cardio protection should provide pharma companies further incentive to develop drugs that can prevent diabetes-mediated clinical complications. We hope that future research in this area will concentrate on exploration of biomarkers that would indicate the progress of the disease, so that appropriate interventions could be developed. We also suggest that instead of the current focus on the management of risk factors, public health experts should initiate screening of individuals at risk, to diagnose impaired glucose tolerance at the population level and develop appropriate interventions to prevent diabetes.

REFERENCES

1. Roth GA, Menash GA, Johnson C, et al: Global Burden of Cardiovascular Disease and Risk Factors, 1990-2019: Update from the GBD 2019 Study. J Am Coll Cardiol 76 (25):2982-3021, 2020.
2. Andersson C, Nayor M, Tsao CW, et al: Framingham Heart Study: JACC Focus Seminar 1/8. J. Am. Coll Cardiol 77 (21):2680-2692, 2021.
3. Jahangiry L, Farhangi M, Rezaei F: Framingham risk score for estimation of 10-years of cardiovascular diseases risk in patients with metabolic syndrome. J Health Popul. Nutr. 2017; 36: 36. Doi:10.1186/s41043-017-0113-0.
4. Yusuf S, Hawken S, Ounpuu S, et al: Effect of potentially modifiable risk factors associated with myocardial infraction in 52 countries (the INTERHEART study): case control study. The Lancet 364 (9438)937-952, 2004.
5. Khera AV, Emdin CA, Drake I, et al: N Engl. J. Med. 2016; 375:2349-2358. DOI:10.1056/NEJMoal1605086
6. Di Cesare M, Bennett JE, Best N, et al: The contributors of risk factor trends to cardiometabolic mortality decline in 26 industrialized countries. Int. J. Epidemiol. 2013; 42(3):838-48. Doi:10.1093/ije/dyt063.
7. Kuulasmaa K, Tunstall-Pedoe H, Dobson A, et al: Estimation of contribution of changes in classic risk factors to trend in coronary-event rates across the WHO MONICA Project. Lancet 2000; 355:675-87. PMID: 107033799.
8. Giacco F, Brownlee M: Oxidative stress and diabetic complications. Cir Res. 2010;107 (9): 1058-70. Doi: 10.1161/CIRCCRESAHA.110.223545.
9. Yuan T, Yang T, Chen H, et al: New insights into oxidative stress and inflammation during diabetes mellitus-accelerated atherosclerosis. Redox Biol 2019; 20: 247-260.
10. Hill TD, White JG, Rao GHR et al: Platelet hypersensitivity induced by 1-cchlordinitrobenzene, hydroperoxides and inhibition of lipoxygenase. Thromb Res.1989; h53(5): 447-55
11. Hill TD, White JG, Rao GHR The influence of glutathione depleting agents on human function. Thromb Res. 1989; 53:457-67
12. Hill TD, White JG, Rao GHR Role of glutathione and glutathione peroxidase in human platelet arachidonic acid metabolism. Prostaglandins 1989; 38:21-32
13. Radha E, Hill TD, Rao GHR et al: Glutathione levels in human platelets display a circadian rhythm *in vitro* Biochem Biophs Res Comm. 1985; 117:549-56
14. Hybertson BM, Gao B, Bose SK, et al: Oxidative stress in health and disease: The therapeutic potential of Nrf2 activation. Mol Aspects of Med. 32:234-246, 2011
15. Rao GHR: Metabolic Diseases Enhance the Severity of Coronavirus Disease. J. Pathos. Infect Dis. 2021; 4(1):1-8. DOI:10.33309/2639-8893.040103
16. Wu J, Huang J, Zhu G, et al: Elevation of blood glucose levels predict worse outcomes in hospitalized patients with COVID-19: a retrospective cohort study. BMJ/open Diab Res. Care 2020,8e001476. Doi:10.1136bmjdrc-2020-001476
17. Kumar P, Osahon Ob, Vides DB, et al: Severe glutathione deficiency, oxidative stress and oxidant damage in adults hospitalized with COVID-19: Implications for Gly NAC (Glycine and N-Acetylcysteine) supplementation. Antioxidants 2022, 11 (1): 50. https://doi.org.10.3390/antiox11010050
18. Aronson D, Rayfield EJ: How hyperglycemia promotes atherosclerosis.
19. Pober JS, Sessa WC: Evolving functions o endothelial cells in inflammation. Nat. Rev Immunol. 2007;7(10): 803-815.
20. Meza CA, La Favor JD, Kim D, et al: Endothelial dysfunction:

Is there a hyperglycemia-induced imbalance of NOX and NOS. Int J. Mol Sci 20 (15):3775, 2019. Doi: 10.3390/ijms20153775

21. Gerrard JM. Stuart JM, Rao GHR, et al: Alteration in the balance of prostaglandin and thromboxane synthesis in diabetic rats. Transl Res. J. Lab Med. & Clin Sci. 95 (6):P950-958, 1980.
22. Bornfeldt KE, Tabas I: Insulin Resistance, Hyperglycemia, and Atherosclerosis. Cell Metabolism 14 (5):575-585, 2011.
23. Booth G, Stalker TJ, Lefer AM, et al: Mechanism of amelioration of glucose-induced endothelial dysfunction following inhibition of protein kinase C in vivo. Diabetes 51:1556-1564, 2002.
24. Fenster A, Blake C, Gyacskov I, et al: 3D ultrasound analysis of carotid plaque volume and surface morphology. Ultrasonics 44: e153-e157, 2006.
25. Spence JD, Solo K: Resistant Atherosclerosis: The need for monitoring plaque burden. Stroke 2017; 48:1624-1629.
26. Spence JD, Hackman DG: Treating arteries instead of risk factors: a paradigm changes in management of atherosclerosis. Stroke 2010;41:1193-1199.
27. Fernandez-Friera L, Fuster V, Lopez-Melgar B, et al: Vascular inflammation in subclinical atherosclerosis detected by Hybrid PET/MRI. J Am Coll Cardiol. 2019; 73(12):137101382.
28. Ridker PM, Everett BM, Thuren T, et al: Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl. J. Med. 2017; 377:1119-1131. DOI: 10.1056/NEJMoa1707914.
29. Zelniker TA, Wiviott SD, Raz I, et al: SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet 2019; 393:31-39. https://doi.org/10.1016/S0140-6736(18)32590-X.
30. Lopaschuk GD, Verma S: Mechanisms of Cardiovascular Benefits of Sodium Co-transporter (SGLT2) Inhibitors. JACC Basic Transl. Sci 2020; 5(6): 632-644. PMID: 32613148.
31. Chen Y, Jandelelt-Dahm K, Peter K: Sodium-Glucose Co-Transporter (SGLT2) Inhibitor Dapagliflozin Stabilizes Diabetes-Induced Atherosclerotic Plaque Instability. J. Am Heart Assoc.2022;0:e022761. https://doi.org/10.1161/JAHA.121.022761.
32. Keys A, Menotti A, Aravanis C, et al: The seven countries study: 2,289 deaths in 15 years. Prevent. Med. 13 9@): 141-154, 1984. Doi:10.1016/0091-7435 (84) 90047-1.
33. Puska P: Successful prevention of non-communicable diseases: 25-year experience with North Karelia Project in Finland. Publ. Health Med. 41 (4):5-7, 2002
34. Rao GHR: The Tsunami of Cardiometabolic Diseases. An overview. J. Diab. & Obesity & Metabolic Syndrome. 1 (1):01-9, 2020.
35. Lin Xi, Xu Y, Pan Xi, et al: Global, regional, and national burden and trend of diabetes in 195 countries and territories: an analysis from 1990 to 2025.
36. Rao GHR: Coronavirus Diseases and Acute Vascular Events. Clin Appl. Thromb. Hemost. 2020; Jan-Dec;26: 10760296209290091.doi:10.1177/1076029620929091. PMID: 327551130.
37. Rao GHR: Coronavirus Disease (Covid-19): A Disease of the Vascular Endothelium. Series Cardiology Res 2020; 2(1): 23-27.
38. Rao GHR: Syndemic of Coronavirus Disease and Metabolic Diseases: global Perspective. EC Endocrinol. Met. Res. 6.4 (2021):28-32
39. Rao GHR: Metabolic Diseases Enhance the Severity of Coronavirus Disease. J. Pathol. Infect. Dis. 2021;4(1):1-8. DOI:10.33309/2639-8893.040103
40. Rao GHR: Coronavirus Disease: An additional Risk Factor for Acute Vascular Events. Diabetes and Obesity Int. J. 2021;(4): 000250.
41. Sancar G, Liu S, Gasser E, et al: FGF1 and insulin control lipolysis by convergent pathways. Cell Met. 34 (1):171-183. https://doi.org/10.1016/j.cmet.2021.12.004
42. Cohn JN, Hoke L, Whitman W, et al: Screening for early detection of cardiovascular disease in asymptomatic individuals. Am Heart J. 2003;146:679-85.
43. Blackburn H: The Contribution of Epidemiology to Cardiovascular Health. In: Coronary Artery Disease in South Asians : Epidemiology, Risk Factors and Prevention. Pp 1-6, (Eds. Gundu H. R Rao and Vijay V Kakkar) Jaypee Medical Publishers, New Delhi, India. 2001. ISBN# 81-7179-811-X.

How to cite this article: Rao G H R. Altered Glucose Metabolism and Acute Vascular Events. J Clin Cardiol Diagn 2022;4(1):9-16.

DOI: 10.33309/2639-8265.040104