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Type-2 Diabetes-Related Chronic Complications

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Commentary

Diabetes as a metabolic disease is known for centuries. Historical perspectives claim, that this disease was known to ancient Egyptians and Indians, thousands of years ago [1]. Despite the fact, that this is one of the oldest metabolic diseases, very little is known on the etiology of the disease, as well as how various chronic complications, such as retinopathy, nephropathy, neuropathy and vasculopathy [2]. In addition to these well know complications, diabetic patients also suffer from skin and foot complications. A large portion of the diabetics have at least one complication present at the time of diagnosis. In recent literature, there are some suggestions about possible relationship between, diabetes and cancer as well as Alzheimer's disease. Million-dollar question is, how hyperglycemia is central to the pathophysiology of chronic complications, such as Alzheimer's Disease, Cancer, Cardiovascular and Peripheral vascular disease, damages to the nerve (neuropathy), damage to the kidney (nephropathy)and damage to the eye (retinopathy). Currently diabetes is diagnosed by the increased levels of blood glucose, or by the elevated HBA1c levels.

Having said that, I would like to inform the readers that despite the fact that this disease is common worldwide, and screening tests are available, the disease remains under-diagnosed. It is a common speculation, that in any given country the pre-diabetic population is equal, or more than the diabetic population. Even in an advanced country like the USA, the pre-diabetic population is twice that of the diabetic population. In terms of diagnosis and management, by and large, in majority of the countries, it is just limited to the measurement of fasting blood glucose, and management of hyperglycemia. Understanding the specific mechanism that underlies these various hyperglycemia-mediated clinical complications, will help clinicians develop personalized, precision medicine for the management of diabetes-related chronic complications.

Since we are discussing early diagnosis of metabolic diseases, it is important to consider the metabolic disturbances that occur during the critical growth period of the fetus. In Asian Countries with huge populations, 30% of the children born are low-birth weight babies. These low-birth weight children, when they reach adolescent and adult age, are "at risk" for developing metabolic diseases [2-5]. Based on studies done in the UK and India, David Barker, a British Epidemiologist developed a hypothesis, that intrauterine growth retardation, low-birth weight, and premature birth, have a causal relationship to the origins of hypertension, coronary artery disease and non-insulin-dependent diabetes in middle age [3,4]. A study conducted by the Department of Nutrition Harvard School of public Health, agreed with systematic reviews showing that maternal micronutrient supplementation, can reduce the risk of having an infant with low birth weight [6].

In view of these observations, we have initiated a bilateral research program, funded by the prestigious National Institute of Health, to explore molecular mechanisms

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involved in the fetal origin of adult diseases. The collaborative study between the staff of Children's National Memorial Hospital, Washington DC, and the researchers of diabetes clinic, KEM Hospital, Pune, India, will explore the role of adipocyte-derived exosomal miRNA, in modulating obesity-related clinical complications [7].

The earliest measurable alterations in the normal metabolism of pre-diabetes, as well as diabetes are; creeping up of increase in the fasting blood glucose levels, increase in body-mass index, and development of impaired insulin sensitivity. According to a recent study, presented by Japanese researchers at the Annual Meetings of the European Association for the Study of Diabetes (EASD) in Berlin, Germany(Oct 2018), these three biomarkers could be used for prediction of future diabetes developments, as far back as 20 years before it occurs. It is believed, that high blood sugar levels reduce the powerful vasodilator of the endothelial system, -nitric oxide in blood vessels, a short fall that increases the risk of high blood pressure, and eventually narrowing of the vessels. The exact mechanism by which elevated blood glucose lowers the vasodilator in the blood vessels is not clear.

Three decades ago, studies in our laboratory at the University of Minnesota, demonstrated that one of the earliest metabolic alterations noticeable, in a drug-induced diabetic animal model was arachidonic acid (AA) metabolism in circulating platelets, and vessel wall endothelium. In this animal model, vessel wall production of the vasodilatory metabolite of AA, prostacyclin (PGI_2) production was compromised. Whereas, the platelet production of proaggregatory, vasoconstrictory metabolites of AA, Prostaglandin endoperoxides (PG: PGG_2/PGH_2), and thromboxanes were increased [8]. Looks like the elevated blood glucose can lower both nitric oxide, as well as Prostacyclin, in the blood vessels, thereby creating an imbalance in the ratio of vasodilator/vasoconstrictor.

Other metabolic alterations, that can also be measured are the development of oxidative stress and the products that are generated (reactive oxygen species ROS), and low-grade chronic inflammation. ROS can directly damage lipids, proteins, and modulate intracellular signaling pathways. Hyperglycemia-induced oxidative stress can also induce endothelial dysfunction, earliest sign of vascular disease, which is known to play a critical role in the pathogenesis of micro- and macro-vascular diseases [9-13].Researchers also have demonstrated that methylglyoxal (MG), a glucose-derived molecule that is overproduced in cells damaged by hyperglycemia, turns on a gene called angiopoetin-2, which plays a central role in the loss of small blood vessels in the retina. In the diabetic retinopathy (DR), the loss of microvasculature causes low oxygen delivery to parts of the retina, which then compensates by stimulating neoangiogenesis. It is the growth of the new vessels that cause intra retinal bleeding. Chinese researchers have identified three microRNA signatures from serum that may serve as noninvasive diagnostic biomarker for diabetic retinopathy [14].

They speculate that DR-associated miRANs may be involved in the pathogenesis of DR at least in part, through modifying proliferation of human retinal microvascualr endothelial cells. Diabetic neuropathy is one of the serious clinical complications. However, we do not have a competent biomarker as yet, similar to micro albumin in diabetic nephropathy, for the diagnosis of diabetic neuropathy [15]. Sudomotor dysfunction is defined as decreased sudomotor activity. Similar to endothelial dysfunction in the prediction of atherosclerosis, the pathological state known as sudomotor dysfunction, is the earliest clinically detectable stage of autonomic neuropathy [9,16] Gandhi and associates using a noninvasive diagnostic platform, performed studies on diabetic patients and determined Sudo Path score, which includes three components of sudomotor function (sweat output, microcirculation response, and sweat gland density) and demonstrated the specificity and sensitivity of this system to determine diabetic neuropathy [17].

Chronic hyperglycemia plays a major role in the initiation of diabetic vascular complications through many metabolic and structural derangements, including the production of advanced glycation end products (AGE). Protein glycation products seem to be the major causes of different diabetic complications. Initial accumulation of AGEs in the vascular tissue could initiate local inflammation, and lead to cell-mediated vascular calcification by activation of RAGE. Hyperglycemia-induced oxidative stress, and the DAG- protein kinase C (PKC) pathway activation, are implicated in the development and progression various vascular complications including diabetic nephropathy [12]. As we have described earlier, in our drug-induced diabetes model arachidonic acid metabolism was promoted towards excess generation of pro-aggregatory prostaglandins via cyclooxygenase pathway as well as 12 (S)-HETE and diacylglycerol via lipoxygenase pathway.

Korean researchers have demonstrated, that some species of PKC-δ and PKC-ε are sensitively activated by hyperglycemia-induced oxidative stress in diabetic rat kidney [18].Diabetes is a chronic complex metabolic disorder. Diabetic vasculopathy is multi factorial disease.

Several studies have pointed out, that advanced glycation end product (AGE) are the leading molecules that cause vascular cell derangement by interacting with specific receptors (RAGE). It has been shown, that when animals are made diabetic, they develop tell-tale signs of diabetic nephropathy and retinopathy [19]. Furthermore, these researchers have demonstrated the role of vascular polysomal poly (A) (+) RNA, a novel splice coding for soluble RAGE protein, called endogenous secretory RAGE. This endogenously secreted molecule was found to neutralize the AGE action on endothelial cells, suggesting that this variant has potential to protect blood vessel from diabetes-related injuries. Another system that seems to play a critical role in the diabetes-related cardiac, vascular, and renal damages is the renin-angiotensin system (RAS).

Increases in RAS activity may lead to the formation of Ang11 in cardiac, vascular and renal tissues and predispose these tissues to further damage. The Key role of angiotensin-converting enzyme (ACE with the RAS system is well established. ACE plays a central role as a pressor enzyme which promotes the formation of vasoconstrictor Ang 11, and inactivates the vasodilator, Ang-1. A further role has also been demonstrated for ACE, as an inactivator of vasodilator Bradykinin, thus the role of ACEas pro-hypertensive enzymes is well established, highlighting the importance of RAS inhibition in the management of diabetes-related complications [19].

We have mentioned in the previous paragraphs, that hyperglycemia is the cause for all the chronic clinical complications of diabetes. I would go one step further and state, that altered blood flow and the resulting damages are responsible for all the diabetes-related chronic clinical complications. Researchers from Tulane University have published data linking high blood pressure to increasing toxicity of the beta-amyloid plaques that are characteristic of Alzheimer's disease. Furthermore, there is some speculation, that constriction of the cerebral vessels and damage of the blood vessels add to this complication. Framingham heart study group have demonstrated that in drug-induced hyperglycemia, one can show altered metabolism of various signaling pathways, including arachidonic acid in platelets and vascular tissue, similar to our earlier studies at the University of Minnesota. Researchers at the Anderson Cancer Center have shown that sugars promote inflammatory pathways. They also have shown excess 12-HETE, a product of AA metabolism, in lung metastasis and breast cancers [20]. Recent studies suggest, a role for glucose-DNA alterations, leading to the development of cancer. There seems to be an association between excess glucose (diabetes) and cancer. Having said that, it is not clear as to why women with diabetes are more prone to get cancer than men?

Skin lesions, irritations, dryness, ulcerations, and diabetic foot are common major complications and are multi factorial, besides hyperglycemia and elevation of advanced glycation end products [20]. Overall prevalence of skin disorder in diabetics, seem to be between 50 to 97% in different regions of the world. In majority of cases, fungal infections seem to be more common than bacterial or viral infections. It is believed, thatgood glycemic control may reduce the incidence and severity of skin disorders, without known pathogenesis. In addition to the skin lesions, diabetic foot pain and ulcers are common complications of poorly controlled glycemia. These lesions usually are formed as a result of skin tissue breaking down exposing the layers of tissues underneath. They are most common under the big toes and the balls of the feet. The majority of foot ulcers appear to result from minor trauma in the presence of sensory neuropathy [21].

The purpose of writing this commentary was not to catalogue all the chronic clinical complications related to type-2 diabetes, but to educate the readers as to how little we know of the underlying causes, for the development of these common diabetes-related complications. As we have mentioned in this article, currently only method of management of these complications, is by robust control of hyperglycemia. There is nothing wrong with it. However, it would be great, if we can encourage additional research of these less known areas, to find out the etiology of these hyperglycemia-mediated complications. I am sure there will be some relationship with gene-gene interactions, gene-environment interactions gene expression of proteins, micro RNAs, activation or inactivation of certain signaling mechanisms, altered immune response, altered blood flow and hypoxia and the progress of these risk factors. Understanding the pathophysiology of these complex processes will provide clinicians a better opportunity to design personalized, precision medicine for caring their patients.

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