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Review: Chronic Kidney Disease and Diabetic Nephropathy - Major Complications of Type 2 Diabetes Mellitus

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Abstract:

Diabetes is one of the most common chronic, non-communicable diseases around the world. The diabetes population is expected to be expanded up to 642 million in 2040 and it has the noteworthy predominance in Asia, Middle East, and Africa, whereas the lowest prevalence of diabetes has been enlisted in North Europe. The International Diabetes Federation detailed in 2011 that diabetes was responsible for about 4.6 million deaths every year, one death after every seven seconds. Type 2Diabetes mellitus has become a major health issue worldwide because it increases the risk for cardiovascular diseases, renal failure, blindness, and peripheral neuropathy. Age, obesity, and sedentary lifestyle are associated with type 2 diabetes mellitus.

There is a growing scientific interest in associating the pathophysiology of diabetes complications with oxidative stress. Experimental and clinical studies conducted so far have revealed that oxidative stress plays a pivotal role in both pathogenesis and in improvement of complications in type 2 diabetes mellitus: nephropathy, neuropathy, retinopathy, and cardiovascular disease. This review describes the oxidative stress associated with Type 2 diabetes mellitus, its relationship to the pathophysiological process in developing diabetic nephropathy which progresses into Chronic Kidney Disease subsequently. Further, we focus on endogenous antioxidant defense mechanisms and aminothiol variations in diabetic nephropathy.

Keywords —Type 2 Diabetes Mellitus, Oxidative Stress, Diabetic Nephropathy, Chronic Kidney Disease

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I. INTRODUCTION

Diabetes is a serious long-term health condition which is among the top ten causes of death in adults. It has a significant impact on the lives and prosperity of the individuals worldwide [1]. The number of diabetes adults in the world has increased up year by year due to sedentary lifestyle population growth and aging [2]. In 2014 the number was 422 million. In 2017, it was 451 million and it anticipated that individuals with diabetes would increase up to 693 million by 2045

[3]. Three quarters of people with diabetes live in middle- and low-income countries [4]. Diabetes has the highest prevalence in Asia, Middle East, and Africa [5, 6]. South East Asia is expected to be the region with highest number of diabetes patients in the world by 2025 [5]

Diabetes Mellitus (DM) could bring up long term tissue damage, dysfunction and entire failure of many vital organs which lead to multiple organ impairment [7]. Type 2 diabetes mellitus(T2DM) which is characterized by hyperglycaemia is the most frequent type of diabetes, accounting for around 90% of all diabetic cases. Recent clinical findings explore that the underlying pathways in the pathogenesis of diabetic complications are mainly due to oxidative stress generated by over production of reactive oxygen species (ROS) during hyperglycaemia and subsequent tissue damage [8]. Diabetic nephropathy (DN) has been identified as a major complication of DM and is more frequently found in T2DM due to the existence of long term, uncontrolled hyperglycaemia [9]. Also, DN has been highlighted as a prominent reason of chronic kidney disease (CKD) and end-stage renal failure worldwide [10]. According to scientific literature, Diabetes mellitus and chronic kidney disease depicts cooperative associations with premature mortality [11].

TYPE 2 DIABETES MELLITUS AS A METABOLIC DISORDER

Type 2 diabetes mellitus is a metabolic dysregulation described by hyperglycemia. It can occur due to reduced insulin secretion, insulin resistance, or a combination of both. Insulin insensitivity, obesity, and decline of pancreas β-cell dysfunction are related to hyperglycemia [12]. It has been suggested that increased non-esterified fatty acids, adipokines, inflammatory cytokines, and mitochondrial dysfunction causes insulin resistance and glucotoxicity, lipotoxicity and amyloid formation for β- cell dysfunction. Since glucose transporters are essential for glucose homeostasis in the body, dysfunctional glucose transport proteins may also play a role in the development of hyperglycemia [13, 14]. Moreover, T2DM is considered to have a strong genetic component.calpain10, potassium inward-rectifier 6·2, peroxisome proliferator-activated receptor γ and insulin receptor substrate-1 are certain genes that identified as related with T2DM. Patients with T2DM have been diagnosed with plasma glucose concentration ≥ 7.0 mmol/L or a 2-hour post glucose load, plasma glucose concentration ≥ 11.1 mmol/L or glycated hemoglobin, HbA1c ≥ 6.5%. DM could bring up long term damage, dysfunction and failure of many vital organs which lead to multiple organ impairment [15]. T2DM has devastating microvascular and macrovascular complications. Long-term T2DM increases the risk for, renal failure (as a result of diabetic nephropathy), cardiovascular diseases, blindness (as a result of diabetic retinopathy), peripheral neuropathy, hearing impairment, skin conditions and sleep apnea.[8, 16].

DIABETES MELLITUS AND OXIDATIVE STRESS

A Chemical species (atom or molecule) which possesses a single unpaired electron is defined as a free radical. Examples: Superoxide, Nitric oxide, Hydroxyl radicals, and lipid proxy radicals. Due to their reactive nature, they can cause selective oxidation of proteins, lipids, and nucleic acids. Thereby they can act as oxidants. Oxidants are species that promote the oxidation of other substances while antioxidants prevent the oxidation of other substances. An imbalance between oxidant (free radical) and antioxidant levels in cells and tissues in favour of oxidants is explained as oxidative stress. Elevation of oxidant level leads to modification of biomolecules like lipids, proteins,

DNA, RNA, and B-Vitamins in the cells and the blood. Such modifications that lead to reduced or changed biochemical functions of the above biomolecules are referred to as oxidative damage [17, 18]. Oxidative stress may arise as a result of reduced antioxidant levels, antioxidant enzymes, or faults in the antioxidant mechanism expressing the antioxidant genes [19].

OXIDATIVE STRESS ASSOCIATED WITH DIABETES MELLITUS.

Several studies have revealed that oxidative stress is increased in type 2 diabetes mellitus, and increased oxidative stress is the fundamental cause of insulin resistance, dyslipidaemia, β-cell dysfunction, impaired glucose tolerance and ultimately leading to T2DM [8, 20, 21]. Oxidative stress has been suggested as one of the main staple mechanisms for developing microvascular and macrovascular complications in diabetes mellitus patients. Mitochondrial overproduction of reactive oxygen species (ROS) such as superoxide due to the metabolic abnormalities of diabetes, cause cellular damages in several ways [8, 20]. It has been suggested that hyperglycaemia causes tissue damage through several biochemical mechanisms such as increased intracellular AGE formation, activated protein kinase C pathway, polyol pathway flux and increased oxidation of fatty acid. Recently it has been theoretically established all the above mechanisms are induced by superoxide overproduction in the mitochondrial electron transport chain [8].

DIABETES MELLITUS, DIABETIC NEPHROPATHY AND CHRONIC KIDNEY DISEASE

Diabetes mellitus is a metabolic disorder known to cause retinopathy, neuropathy, and nephropathy. Complicationsof DM develop gradually with time due to prevalence of long-term hyperglycaemia along with less controlled blood glucose levels. Recent clinical findings explore that the underlying pathways in the pathogenesis of diabetic complications comprise of oxidative stress generated by the over production of ROS and abnormalities in the insulin signal transduction pathway [7]. Diabetic nephropathy has been highlighted as a prominent cause of chronic kidney disease and end-stage renal failure globally [10]. According to literature, Diabetes mellitus and chronic kidney disease exhibit cooperative associations with premature mortality. Therefore in UK, current diabetic guidelines recommend annual urinary albumin and serum creatinine investigations for diabetic patients to screen for kidney diseases [11].

Diabetes along with insulin resistance can heavily trigger microvascular complications of diabetes, especially diabetic nephropathy (DN). Hyperglycaemic control has been suggested and is the most effective way to prevent the development and progression of diabetic nephropathy. Out of many factors which leads to the development of DN, inflammatory- or oxidative-stress-induced basis for development of DN has been obtaining the interest today. Other risk factors include age, diet, obesity, or lifestyle. Further, recent findings shows that potential endogenous protective factors could possibly decrease the effect of inflammation and oxidative stress, showing great support for the treatment of DN patients [22].

DN patients are seen in 20% - 40% of all diabetics [23]. Diabetic nephropathy ultimately developing to CKD can be considered as a common complication seen in the diabetic populations; high prevalence of CKD has been observed in populations with type 2 diabetes. And the reasons behind chronic kidney disease is likely to be any of the following: type 2

diabetes, hypertension, IgA based nephropathy or any combination of above [24]. And also emerging evidence suggests that diabetic nephropathy is one of the major complications of DM that leads to end stage renal disease (ESRD) [25, 26]. Is recognized as the renal disease caused by insult to tiny capillaries in the kidney's glomeruli. It is mainly caused by microvascular dysfunction where the basement membrane of glomerulus undergo thickening. Although morbidity and mortality of diabetic patients are considerably aggravated due to cardiovascular complications, DM has significantly affected kidney and urinary tract. As, approximately 40% of patients requiring dialysis around the world suffer from DM as the responsible cause, diabetes accounts for most cases of ESRD [22].

CHRONIC KIDNEY DISEASE AND STAGES

Chronic kidney disease is considered as a major cause of global morbidity and mortality [27]. The term CKD is generally used to describe a set of medical complications which affecting morphological and physiological aspects of the kidney [28, 29]. Scientific literature suggests many but analogous definitions to define the term CKD. Literature has defined Chronic Kidney Disease as a permanent kidney damage or as a reduction in glomerular filtration rate (GFR) less than 60 mL/min/1.73 m^2 for consecutive 3 months or more, irrespective of the origin [30]. Similarly, CKD is defined as the prevalence of Kidney damage (defined in the terms of structural or functional abnormalities of the kidney) for three or more months, along with or without reduced GFR. This is manifested by pathological abnormalities or markers of kidney damage such as derangements in the composition of the blood or urine or anomalies in imaging tests [31].

About 10 - 15% of adult population across the globe is suffering from CKD while it being one of the top leading causes of death in USA. Global prevalence of CKD is escalating rapidly where the prevalence in Asian continent varies from 10-18% of its population. Prevalence of CKD in other parts of the globe is not much different from Asia [29]. At present, Chronic kidney disease has been recognized as a major public health problem worldwide, with a variety of adverse outcomes such as kidney failure, cardiovascular disease, and premature death [32]. At present there are over 1.4 million cases under kidney replacement therapy [33].

CKD tends to progress slowly over months and years without depicting any symptoms. Appearance of symptoms may not take place until kidney becomes one-tenth of its original function .Therefore, early diagnosis and rapid execution of medical interventions is crucial as most of medical interventions tends to become inefficient if disease proceeds to more serious stages [29].Variety of etiologies are responsible for progression where diabetes mellitus being predominant due to enormously increased possibility of causing micro and macrovascular damages [33].

KDOQI (Kidney Disease Outcomes Quality Initiative) guidelines on CKD published by the National Kidney Foundation (NKF) in 2002 were formulated based on covering CKD evaluation, classification, and stratification of risk. The panel involved in the process of developing these guidelines has provided the essential supporting structure for a diagnosis of cause- independent chronic kidney disease. Also, they have come up with a classification system of severity depending on the glomerular filtration rate (GFR). With the implementation of this new system, certain noteworthy conceptual changes came out since historical classification had been done based on the cause. New conceptual definition was developed on three major components. They are, availability of

biochemical markers of renal damage(structural), glomerular filtration rate (functional) and occurrence of above structural and/ or functional abnormalities for at least three months [32].

Therefore, diagnosis of CKD depends on the availability of biochemical markers of renal damage and/or a reduction in glomerular filtration rate. Classification and Staging criteria are as in Table 1 according to KDOQI guidelines and Modified and Endorsed by KDIGO (Kidney Disease: Improving Global Outcomes).

TABLE I
CLASSIFICATION OF CKD AS DEFINED BY KDOQI AND MODIFIED AND ENDORSED BY KDIGO

Stage	Description	GFR (mL/min/1.73 m^2)
	At increased risk	≥ 90 (with CKD risk factors)
1	Kidney damage with normal or ↑ GFR	≥ 90
2	Kidney damage with mild ↓ in GFR	89-60
3	Moderate ↓ in GFR	59-30
4	Severe ↓ in GFR	29-15
5	Kidney failure	< 15 (or dialysis)

DIABETES MELLITUS, CHRONIC KIDNEY DISEACE AND AMINOTHIOLS

Concentrations of aminothiols that are considered as redox biomarkers: Glutathione (GSH), homocysteine, cysteine, cysteinyglycine, methionine, SAM, SAH, vary in type 2 diabetes mellitus patients. GSH is a tripeptide composed of glutamate, cysteine, and glycine. GSH is one the most important aminothiol in plasma. De novo synthesis of GSH requires three amino acids, cysteine, glutamic acid, glycine, and succeeding actions of two ATP dependent enzymes called Y glutamylcysteine synthetase (Y-GCS) and glutathione synthetase. The amino group of cysteine and carboxyl group of gamma glutamic acid form a specific gamma peptide bond and form Y-glutamylcysteine via the process catalyzed by Y-GCS. Y-glutamylcysteine with glycine forms GSH by GSH synthetase. Antioxidant property of GSH is based on the presence of cysteine thiol group. Bioavailability of cysteine is the rate-limiting factor of GSH synthesis process (Townsend, Tew et al. 2003).

The endogenous antioxidant system which protects the cells from oxidative damage is mainly based on glutathione (GSH-Gamma glutamylcystinylglycine). During the free radical attack glutathione (GSH) act as an electron or hydrogen donor (Meister 1988). Thereby it neutralizes free radicals. In that process, glutathione is converted to its oxidized form called glutathione disulphide (GSSG) and this step is catalyzed by glutathione peroxidase (GPx) (Townsend, Tew, et al. 2003). The reduction of the glutathione disulphide to its thiol form is catalyzed by the Glutathione reductase (GSR) while oxidizing NADPH. During oxidative stress, GSR expression is regulated in both transcription and post-translational modification levels [34].

Cysteine (Cys) is a sulfur containing amino acid that is nutritionally semi-essential (Yin, Ren, et al. 2016). Due to the presence of a sulfhydryl group(S-H) this amino acid is considered a chemically reactive amino acid. It can form intermolecular disulfide linkages which in turn maintain protein structure and stability (Elshorbagy, Smith, et al. 2012) [35]. It can also act as an antioxidant and is the limiting factor in synthesis of glutathione (GSH) (Townsend, Tew, et al. 2003). Changes in the concentration of extracellular cysteine levels lead to oxidative stress and other pathological disorders (Elshorbagy, Smith et al. 2012).

Catabolism of methionine break down from endogenous proteins and absorption from diet collectively gives rise to cysteine pool in the body. During methionine degradation pathway first methionine get condensed with adenosine tri phosphate (ATP) and giving rise to S-Adenosylmethionine (SAM). This reaction is catalyzed by adenosyl methionine synthetase. Then SAM transfer its methyl group to a methyl acceptor (ex-norepinephrine) via methyltransferase forming S-Adenosylhomocysteine (SAH). SAH is hydrolyzed to homocysteine and adenosine. Synthesized homocysteine will be condensed with

serine to form cystathione, catalyzed by cystathione β-synthase. Finally, cystathione is converted to cysteine by Y-cystathionase. Cysteinylglycine (CG) is a dipeptide with a sulfhydryl group. It possesses the ability to act as an oxidant [36]. Degradation of reduced form of glutathione gives rise to cysteinylglycine and glutamic acid, catalyzed by gamma glutamyltransferase (GGT). This process occurs on the cellular surfaces as GGT enzyme located on outer surface of the cell membrane. Formed cysteinylglycine further hydrolyzed to cysteine and glycine by peptidases and are reused for GSH synthesis [37].

In blood, the low molecular weight aminothiols exist in three forms: free reduced (-SH), free oxidized (-S-S-) and protein-bound oxidized (P-S-S-) forms [38]. It has been suggested that redox aminothiol status is a component of antioxidant system in the plasma [39]. The ratio between the concentration of free oxidized aminothiols and reduced aminothiols reflects the level of aminothiol oxidative stress. Particularly, homocysteine that is an oxidant may play a role in aminothiol oxidative stress. Plasma homocysteine levels were higher among T2DM patients with retinopathy and nephropathy than in T2DM patients without retinopathy nephropathy. A significant correlation was observed between homocysteine with age of the patients as well as the duration of diabetes [40]. Buyssschaert et al. found in their study increased plasma total homocysteine (tHcy) level was significantly related with prevalence of nephropathy and macroangiopathy in T2DM patients and this elevated tHcy levels not associated with different degree of insulin resistance.[41]. Lutchmansingh et al showed that T2DM patients have lower glutathione concentration and lower absolute synthesis rates than healthy controls. They further revealed that Glutathione concentrations were lower in T2DM with known microvascular complications compared to controls [42].

II. CONCLUSIONS

In this review we discussed possible evolution of CKD through DN in type2 diabetic mellitus patients. Occurrence of CKD as a major, post complication in type 2 diabetes mellitus is directly linked with oxidative stress. Thereby oxidative stress plays a key role in both pathogenesis and development of CKD and ESRD in type 2 diabetes mellitus patients. We suggest, in future, diabetic mellitus related nephropathy and subsequent CKD should be addressed in terms of oxidative stress and accountable specific biomarkers must be explored to ensure early diagnosis. If identified earlier, adverse health ramifications suffered by diabetes mellitus patients due to DN and CKD would be diminished through early medical interventions. Aim of this review is to motivate future researchers to explore more and more related biomarkers to ensure early diagnosis.

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