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Sialic acid in Diabetic Nephropathy

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Abstract

Diabetic nephropathy (DN) is the leading cause of end-stage renal disease worldwide. Chronic hyperglycemia and high blood pressure are the main risk factors for the development of DN. In general, screening for microalbuminuria should be performed annually, starting 5 years after diagnosis in type 1 diabetes and at diagnosis and annually thereafter in type 2 diabetes. Standard therapy is blood glucose and blood pressure control using the renin-angiotensin system blockade, targeting A1c < 7%, and <130/80 mmHg. Regression of albuminuria remains an important therapeutic goal. However, there are problems in diagnosis and treatment of nonproteinuric DN (NP-DN), which does not follow the classic pattern of DN. In fact, the prevalence of DN continues to increase, and additional therapy is needed to prevent or ameliorate the condition. In addition to conventional therapies, vitamin D receptor activators, incretin-related drugs, and therapies that target inflammation may also be promising for the prevention of DN progression. High serum sialic acid level suggests the underlying inflammatory mechanism in diabetic nephropathy before onset of albuminuria. Sialic acid is suggested to be a reliable predictor for diabetic nephropathy in type 2 diabetic patients.

Keywords: Sialic acid, Diabetic Nephropathy. Diabetes.

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1. Introduction

Sialic acids are a diverse family of sugar units with 9-carbon backbone and typically found attached to outer most ends of these glucoconjugates chains they have particular physicochemical properties. They modulate biological functions of the molecules that carry them [1] Figure 1. Term “sialic acid” first appeared in 1952 to describe N-acetylneuraminic acid as main product released during mild acid hydrolysis of brain glycolipids or salivary mucins [2-3]. Sialic acids (SA) are of neuraminic acid derivatives; they occupy a terminal position in chains of monosaccharide residues of various glycoconjugates. More than 80 members of the SC family, which have various substituents in amino or hydroxyl groups [4]. Substituents mostly found in positions 4, 5, 7, 8, and 9. Substituent at position number 5 is functional group. These include N-acetylneuraminic acid (Neu5Ac) functional group is acetyle group, N-glycolylneuraminic acid (Neu5Gc) functional group is glycoyl group.

2-keto-3-deoxynononic acid (KDN) the functional group is hydroxyl group. In humans Neu5Ac predominates [3] Figure 2. These negatively charged monosaccharides commonly occur as terminal and sometimes as internal residues in glycoconjugates (e.g. glycoproteins, glycolipids, lipooligo/lipopolysaccharides, capsular, and tissue polysialic acids) and carbohydrates (e.g. oligosaccharides, exopolysaccharides). Due to their terminal presentation on cell surface glycans, they facilitate numerous key biological functions related to cellular recognition, cell adhesion, communication/signaling, control of glycoconjugate half-life in circulation, tumor growth and metastasis, and developmental programming. NulOs also have key roles in immune regulation, as well as host interactions with viruses, bacterial pathogens, and the microbiota, including commensals, symbionts, and opportunistic pathogens [5].

2. Expression of linkages and modifications of Sias

Certain linkages and modifications of Sias typically show tissue-specific and developmentally regulated expression. Some linkages and modifications are even molecule-specific, that is, they are found only on certain types of glycoconjugates in a given cell type. Even within a particular glycoconjugate group, a modification such as O-acetylation may be restricted to certain Sia residues at particular positions on a glycan [5]. Such findings indicate the occurrence of specific enzymatic mechanisms for generation and regulation of Sias; they also suggest specific roles for these linkages and modifications. On the other hand, available evidence indicates substantial species-specific variations in the cell- and tissue-type distribution of different Sia linkages and modifications [4]. Thus, at least some of this regulated expression may be unrelated to intrinsic functions

of Sias. Rather, it may be signature of the evolutionary history of a species in relation to Sia-binding preferences of its pathogens and/or symbionts. Effectively, each species expresses a distinct "sialome," a term defined as total array of sialic acid types and linkages expressed by a particular organelle, cell, tissue, organ, or organism [6]. Of course, unlike genome, is same in every cell type of an organism and undergoes very few changes during lifetime of organism, sialome differs among cell types and varies markedly with regard to time, space, and environmental cues [7].

3. General functions of sialic acids

The high expression of Sias on outer cell membranes (e.g., more than 10 million molecules per human erythrocyte) on interior of lysosomal membranes and on secreted glyco-proteins (such as blood proteins and mucins) suggests that they have roles in stabilization of molecules and membranes, as well as in modulating interactions with environment [8]. Some functions arise from relatively strong electronegative charge of Sias, for example, binding and transport of ions and drugs, stabilizing conformation of proteins including enzymes, and enhancing viscosity of mucins. Sias can also protect molecules and cells from attack by proteases or glycosidases, extending their lifetime and function [5] Figure 3. Furthermore, Sias can regulate affinity of receptors and reported to modulate processes involved in trans-membrane signaling, fertilization, growth, and differentiation. In one system, apoptosis reported to be inhibited by Sia O-acetylation. A recently described general property of Sias seems to be their free-radical scavenging anti oxidative effect, which could be particularly significant on endothelia of blood vessels [10]. Another prominent role of Sias is dualistic; they act either as masks or recognition sites. In first case, they mask antigenic sites, receptors, and, most importantly, penultimate galactose residues. After Sia loss, molecules and cells can be bound, for example, by macrophages and hepatocytes, and can be taken up and degraded [11]. On other hand, Sias themselves can serve as ligands for variety of microbial and animal lectins. Chemical modification of Sias can strongly influence all of these properties, in particular ligand functions. For example, 9-O-acetylation or N-acetyl-hydroxylation of Neu5Ac can create new receptor functions or decrease affinity of binding [4].

4. Sialic acids in pathology and pharmacology

Because Sias involved in so many cellular functions, disturbances of their biosynthesis or degradation can lead to medical problems. Because of their exposed position, Sias are vulnerable to action of microbial esterases, sialidases, and lyases [12]. Actions of these enzymes can affect amount of ligand present, masking of antigenic sites, stabilization of membranes, and immunological and other functions of Sias. In this regard, microbial lectins, sialidases, and trans-sialidases are potent virulence factors. Many bacterial toxins (e.g., cholera, tetanus, and pertussis toxins) and species of virus (e.g., influenza viruses) bind to sialylated glycoconjugates [13]. Bacteria may create new binding sites by sialidase-mediated unmasking of penultimate galactose residues. Trans-sialidases of some pathogenic trypanosome species make these parasites fitter for survival in vector or host, and they strongly disturb host's immune system by compromising cytokine network and influencing signaling processes [6]. Changes in Sias have also found to be involved in degenerative diseases such as atherosclerosis and diabetes as well as neurological disorders such as Alzheimer's disease and alcoholism. Mucins also have to be properly and highly sialylated in order to exert their physiological functions as lubricants and in innate immunity [5].

5. Sialic acid in DN

Diabetes Mellitus (DM) is a disorder of multiple aetiologies, where alteration is characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both [14]. Chronic hyperglycaemia of diabetes associated with significant long-term sequelae, particularly damage and/or dysfunction and failure of various organs, especially kidneys, eyes, nerves, heart and blood vessels [15]. Sialic acid [SA], a generic term for a family of acetylated derivatives of neuraminic acid, is an essential component of glycoproteins and glycolipids. It acts as a co-factor of many cell receptors and is positively associated with most of serum acute phase reactants. In patients with type-2 diabetes mellitus levels of sialic acid are increased [16]. Sialic acid is a component of cell membranes and vascular permeability is regulated by sialic acid moieties. Vascular endothelium carries a high concentration of sialic acid, hence extensive microvascular damage accounts for its shedding into circulation leading to increased vascular permeability & overall increased sialic acid concentration [6].

Thus, elevated levels indicate excessive damage of vascular cells of retina of eyes, kidneys, heart and brain. This leads to conditions like retinopathy, nephropathy and neuropathy [17]. Tissue injury caused by diabetic vascular complications stimulates local cytokine secretion from cellular infiltrates, such as macrophages and endothelial cells. This induces an acute phase response with release of acute phase glycoproteins with sialic acid from liver into general circulation leading to their increased levels [8]. It has proposed that elevated glucose levels promote inflammatory process that seems to play an important role in the development of diabetes and its late complications. In diabetes, acute phase reactants are considered as indicators of microvascular angiopathy [15]. Sialic acid is a component of cell membranes and the elevated levels may indicate excessive cell membrane damage, but more specifically to the cells of vascular tissue.

If there is damage to vascular tissue, this leads to ischaemia and this ischaemia is most visible in the smallest blood vessels, including those of the retina of the eyes, kidneys, heart and brain [7]. It is this ischaemia that leads to conditions including, but not limited to retinopathy, nephropathy and neuropathy. In addition, the serum sialic acid is one of the markers for inflammation and sialic acid can be used as a measurement of acute phase response because many of proteins of immune response are actually glycoproteins and these glycoproteins have sialic acid as terminal sugar on their oligosaccharide chain [16]. In the diabetic nephropathy, there is greater increase in the sialic acid due to damage of the vascular endothelial cells of the kidney and it is considered as a newly established potential risk factor for development of diabetic nephropathy. Therefore, estimation of the sialic acid levels may prove to have predictive value and may have a role in prevention of the microvascular diseases and their complications, in people with the type-2 diabetes mellitus [5].

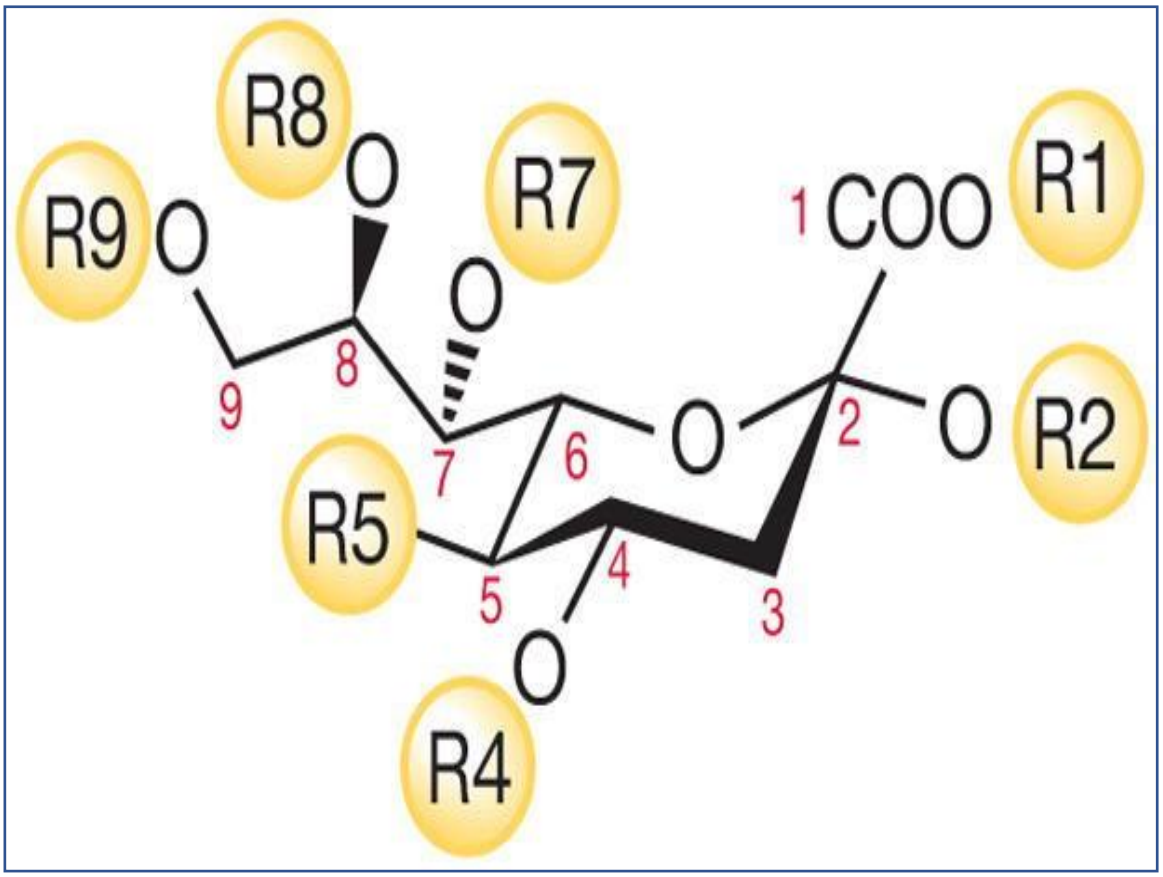

Figure (1): The nine-carbon backbone common to all known Sias [2].

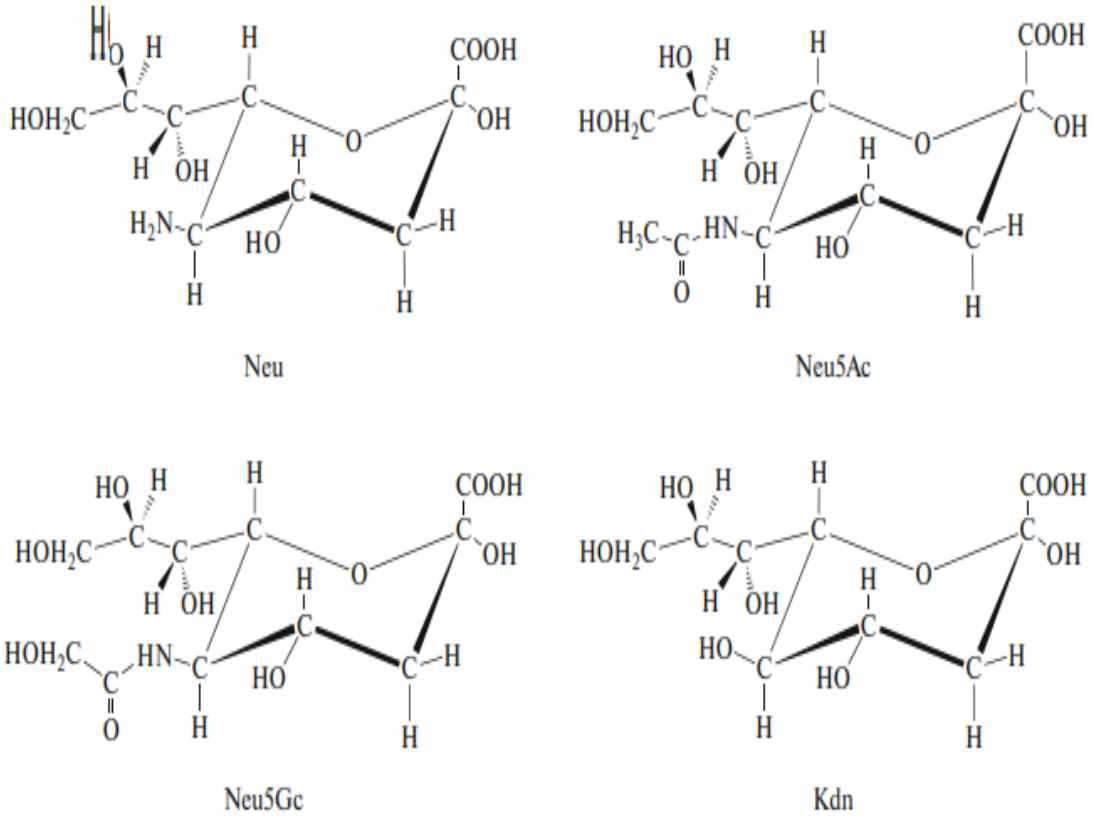

Figure (2). Neuraminic acid and primary sialic acids. Neu—neuraminic acid: Neu5Ac—N-acetylneuraminic acid: Neu5Gc—N-glycolylneuraminic acid: KDN—2-keto-3-deoxynononic acid [3].

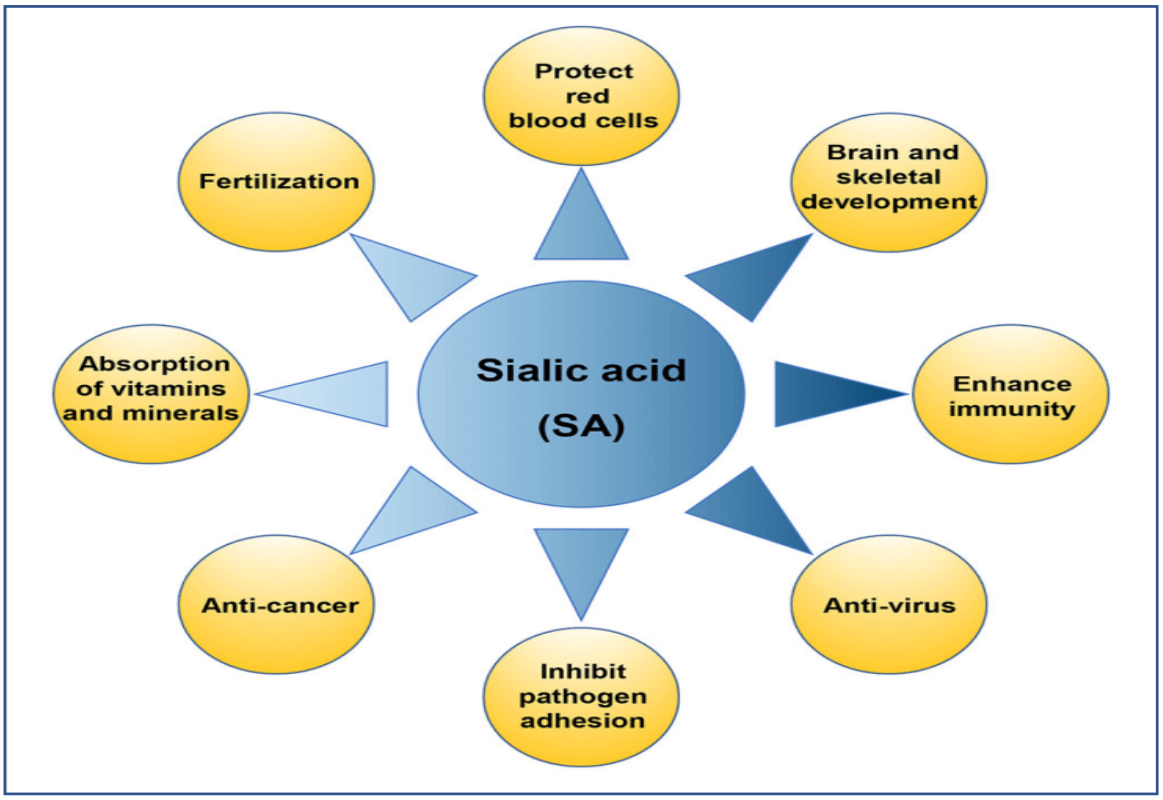

Figure (3): The physiological function of sialic acid (SA) [9].

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