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Association between Pentosidine and Renal Resistence Index with Diabetic Nephropathy

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Abstract

Diabetes mellitus was investigated with different complications that include osteoporosis, neuropathy, and nephropathy. Diabetic renal disease, termed as diabetic nephropathy (DN), is considered as a popular complication of diabetes and is the major source of renal disease that raises diabetic patient morbidity and mortality. DN morphological anomalies involve early glomerular hypertrophy, thickening of the membrane glomerular basement, loss of podocytes, extension of the mesangial matrix, and tubular damages Diabetic nephropathy (DN) is a principle cause of microangiopathy and the main reason for kidney disease at the end stage in patients with type 2 diabetes mellitus (T2DM). Pentosidine was well described as a biomarker for the production and accumulation of AGEs that are to play an important role in diabetes and vascular disorders. Checking diabetic patients with the use of pentosidine would provide a strong long-term glycemic management tool that can have a significant impact on the levels of glycated hemoglobin. The renal resistive index (RI) and pulsatility index (PI), measured using Doppler ultrasonography, reflect intrarenal vascular resistance. We evaluated the relationship between Pentosidine and these indices, which reflects atherosclerosis, and determined whether renal RI differ depending on the underlying renal disease.

Keywords: Pentosidine and RRI with DN.

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1. Introduction

One of the primary aging phenomena in both humans and animals is the increased resistance of collagen, the primary extracellular matrix component, to enzymatic cleavage. This results in decreased solubility, elasticity, and permeability, along with increased thermal stability and stiffness [1]. Additionally, collagen progressively accumulates fluorescent, yellow, and brown substances. These physical and chemical changes suggest the formation of progressive cross-links, and various hypotheses have been proposed to explain their origin. Observations indicate that reducing sugars can react with amino groups of long-lived proteins, producing highly yellow and fluorescent adducts and cross-links through a process known as the nonenzymatic browning or the Maillard reaction [2]. In the Maillard reaction, reducing sugars react nonenzymatically with free amino groups of proteins, initially forming a Schiff base that rearranges into a stable Amadori product. This product undergoes further reactions, resulting in insoluble, highly cross-linked, yellow, and fluorescent products. In the early 1960s, researchers hypothesized that reducing sugars could react with collagen, forming intra- and intermolecular cross-links that stabilize mature collagen fibers. Interest in this area re-emerged in the 1970s, with a focus on nonenzymatic glycosylation, the initial stage of the Maillard reaction [3].

Studies noted increased levels of nonenzymatic glycosylation in diabetic humans and animals, proposing that advanced stages of the Maillard reaction contribute to the aging of long-lived proteins, including lens crystallins and collagens. The excess sugar in diabetes was suggested to accelerate the aging process and contribute to the early onset of conditions such as cataracts and atherosclerosis. Evidence supporting this hypothesis included observations of increased nonenzymatic glycosylation in diabetic and aging individuals, leading to collagen-linked fluorescence [4]. Despite the readily explained age-related acceleration of collagen browning by the Maillard reaction, uncertainties about the exact nature and origin of collagen's autofluorescence prompted a study to elucidate the structure of the fluorescent compounds. This study led to the fractionation of collagen into fluorescent peptides and the discovery of the fluorescent amino acid named pentosidine.

Subsequent reviews will discuss recent studies describing the biomedical significance of pentosidine [5]. The renal resistive index (RRI) is a defined ratio obtained from Doppler measurements in the main renal and intrarenal arteries, representing the difference between maximum and minimum flow velocity divided by the maximum flow velocity. Duplex sonography, a noninvasive method, is commonly used to investigate renal morphologic characteristics. In adults, normal RRI values typically range from 0.47 to 0.70, with a minimal difference between the two kidneys [6]

RRI is closely associated with renal arteriolosclerosis and serves as an integrated index reflecting arterial compliance, pulsatility, and downstream microvascular impedance. While initially considered an indicator of dynamic or structural changes in intrarenal vessels, mounting evidence highlights the impact of both intra and extra renal determinants on RRI, linking it to overall cardiovascular outcomes. Renal and systemic factors, including renal interstitial and venous pressure, aortic stiffness, and pulse pressure, significantly affect RRI [7]. Consequently, RRI not only predicts renal prognosis but also provides insights into general atherosclerotic damage, establishing itself as a well-recognized marker of renal vascular and interstitial damage, indicative of an increased total cardiovascular risk [8]. Given that diabetes mellitus affects both micro and macro vasculature, RRI measurements have been performed in various studies involving patients with diabetes, particularly focusing on type 1 diabetes. The existing literature on RRI and type 2 diabetes is diverse, with studies varying in inclusion criteria, RRI measurement techniques, and overall study design [9].

1.1. Association between pentosidine with DN

Pentosidine, an advanced glycation end product (AGE), has emerged as a potential biomarker for early prediction of DN in children with type 1 diabetes mellitus (T1DM). Studies have shown that elevated pentosidine levels correlate with the duration and severity of hyperglycemia, reflecting the extent of tissue damage in DN. Pentosidine accumulates in renal tissues and urine of individuals with DN, suggesting its role in the pathogenesis of the disease [10].

1.2. Association with disease progression

Research indicates that pentosidine levels are elevated in patients with DN compared to those without renal complications. Longitudinal studies have demonstrated a positive correlation between pentosidine levels and the progression of renal dysfunction in pediatric T1DM patients. Elevated urinary pentosidine levels have been found to precede the onset of microalbuminuria, an early marker of DN, in children with T1DM. Therefore, measuring pentosidine levels may aid in the early identification of children at risk of developing DN [11].

1.3. Clinical implications

Incorporating pentosidine assessment into routine clinical practice may facilitate early detection and management of DN in pediatric T1DM patients. Monitoring pentosidine levels over time can provide valuable insights into disease progression and response to treatment. Additionally, pentosidine levels may serve as a useful tool for risk stratification and guiding personalized therapeutic interventions in this vulnerable population [12]. Further research is warranted to validate the utility of pentosidine as a predictive biomarker for DN in pediatric T1DM patients. Longitudinal studies are needed to assess the effectiveness of interventions targeting pentosidine levels in preventing or delaying the progression of DN. Additionally, elucidating the precise role of pentosidine in the pathogenesis of DN will provide valuable insights into its diagnostic and therapeutic potential [13].

1.4. Association between RRI with DN

Some studies exclusively enrolled type 1 diabetes patients, while others included both type 1 diabetes and control groups or extended to incorporate hypertensive patients [14]. The measurement of the RRI has been predominantly performed in inter lobar arteries, with some measurements taken from segmental and arcuate arteries. While most studies are cross-sectional, a few have a prospective design. The results from these studies are diverse, with associations between RRI and urinary albumin excretion, kidney function, age, diabetes duration, HbA1c, and blood pressure showing inconsistency [7].

1.5. Pathophysiology of increased RRI in type 1 diabetes

Studies have consistently demonstrated an increased RRI in patients with type 1 diabetes compared to healthy and hypertensive individuals. Several mechanisms may contribute to this elevation. Firstly, diabetes affects both the microcirculation (intrarenal) and macrovascular system. As renal dysfunction progresses, microcirculatory alterations occur, leading to an increase in RRI values. Secondly, diabetes can impact the macrovascular system, contributing to renal arteriolosclerosis and chronic hypoperfusion. This can result in damage to renal parenchyma, reducing renal volume and increasing interstitial and vascular resistances, ultimately leading to a higher RRI. Additionally, vascular stiffness in type 2 diabetes, as measured by parameters like aortic pulse wave velocity, has been associated with elevated RRI [15]. The RAS may play a role in RRI elevation, as evidenced by studies showing a significant decrease in RRI after the captopril test in type 2 diabetes patients.

Metabolic syndrome, characterized by increased visceral fat and insulin resistance, could be another explanation. Studies have indicated a correlation between RRI and insulin resistance in type 1 diabetes patients. Furthermore, the presence of metabolic syndrome, especially when associated with type 1 diabetes, has linked to higher intrarenal resistances, as assessed by RRI [15]. The relationship between RRI, albuminuria, and creatinine clearance varies across studies. Presence of renal macrovascular lesions without microvascular lesions may explain the diverse relationships observed. Additionally, tubulointerstitial injury may contribute to increase RRI without an accompanying rise in urinary albumin excretion. Timing of correlation between RRI and albumin excretion may be stage-dependent, with RRI possibly being associated with albumin excretion only in later stages when albumin excretion reaches a certain limit [16].

1.6. The renal volume and RRI

The renal volume/RRI ratio has been suggested as a potential marker for identifying patients at greater risk. Experimental studies indicate that renal enlargement precedes renal hyperfunction in the early phases of

experimental diabetes. In humans, renal hypertrophy and an increase in RRI may represent two different phases of diabetic nephropathy, where renal enlargement is a prealbuminuric reversible step, and increased RRI indicates disease progression with renal scarring before the appearance of albuminuria. Studies have shown that patients with type 2 diabetes have higher mean renal volume, renal area index, and RRI values, but the correlation between mean renal volume, renal area index, and RRI is not consistently observed [17]. In hypertensive patients, a lower renal volume/RRI ratio has been associated with an increased risk of developing diabetes. These findings suggest that the relationship between renal volume and RRI may be complex and could potentially aid in identifying patients at higher risk for adverse renal outcomes [17].

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