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Osteoinductive Factor and Diabetic Nephropathy in Type 2 Diabetes Mellitus Patients: A Literature Review

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Abstract:

Diabetic kidney disease comprises a multifaceted etiopathology that includes glomerular hemodynamic changes, inflammation, oxidative stress, interstitial fibrosis, and tubular atrophy. Diabetic nephropathy (DN), or the pathological alterations in the capillaries caused by diabetes mellitus (DM), is the major cause of end-stage renal disease in diabetic individuals worldwide. Proteinuria, among other elements, as a diagnostic biomarker for DN, is a late change, and so does not detect controlled early nephropathic alterations. This needs the development of novel biomarkers that are more sensitive, specific, and early than proteinuria. Endothelial dysfunction and atherosclerosis are caused by DM, whereas glomerular hypertrophy, an increase in the extracellular matrix, and glomerular sclerosis are caused by DN. Osteoglycin/Osteoinductive Factor (OGN) is a secretory small leucine-rich matrix/basement proteoglycan that regulates lipid and glucose metabolic activity, collagen fibrillogenesis, and cytokine availability in a paracrine/endocrine manner, and has been linked to the development of atherosclerosis, neovascularization, and angiogenesis. OGN is a pathogenic effector and biomarker that is extremely relevant to DM and DN because of these properties. OGN appears to be a better biomarker for DN than microalbuminuria, according to research. This literature review is intended to offer the most recent findings relevant to OGN's DN biomarker potential.

Keywords: Osteoglycin, Osteoinductive factor, Diabetes, Biomarkers, Diabetic nephropathy.

Introduction

Diabetes mellitus (DM) is the amalgam ation of various metabolic illnesses ch aracterized by chronic hyperglycemia. A disturbance in insulin secretion, insu lin effect, or both is typically the cause (1). Polyuria, polydipsia, weariness, w eight loss, visual impairments, infectio n susceptibility, and macro and microv ascular illnesses are all symptoms of se vere hyperglycemia.

Ketoacidosis or non-ketotic hyperosmolar syndrome complicates poorly controlled diabetes, increasing the risk of coma. Long-term damage and functional abnormalities of different tissues and organs (eyes, kidneys, nerves, heart, and blood vessels) are commonly connected with chronic hyperglycemia [(2)]. Type 2 diabetes mellitus (T2DM) is the most common type of diabetes in adults, accounting for over 90% of all occurrences [(3)]. Diabetic nephropathy (DN), commonly known as "diabetic kidney disease (DKD)," is one of the most serious diabetic microvascular consequences, with a

peak incidence between 10 to 20 years after the onset of the disease [4]. DN affects approxim-ately 40% of diabetic individuals and is the major cause of chronic kidney d-isease (CKD) and end-stage renal dise-ase (ESRD) worldwide, particularly in high- and middle-income nations [5]. Because of the high morbidity and mortality associated with DN, much effort has gone into detecting it at an early stage. Albuminuria is a prominent clinical sign for predicting the onset and prog-ression of DN. This classic DN ma-rker, on the other hand, lacks both sensitivity and specificity for detecting the early stages of DN [6]. Patients with DN and ESRD may not have sub-stantial albuminuria. Prior to the disco-very of microalbuminuria, evidence of pathogenic alterations was reported. Furthermore, the lack of a clear link between albuminuria and glomerular filtration rate (GFR) suggests that an alternative to the albuminuria-based staging method is required [7,8].

Osteoinductive factor (OIF), Osteoglycin (OGN), or Mimecan is a tiny leucine-rich repeat proteoglycan found in the extracellular matrix (SLRP). It got its name since it was discovered to stimulate ectopic bone development after being isolated from bovine bone. OGN is a protein that is found in the normal vascular matrix and plays a key function in lipid and glucose metabolism [9]. Angiogenesis and the VEGFR/AKT signaling path-way are both influenced by OGN [10,11]. In T2D patients, circulating OGN levels rise gradually and independently as the severity of kidney impairment increases [12]. As a result, OGN has recently been proposed to have a role in the glomerular pathology associated with DN in T2DM patients as a signal of earlier-stage DN. [12,13].

The objective of this review was to explore the role of OIF in the path-ogenesis and management of DN as a potential early biomarker for comp-lications in T2DM patients. To achieve this goal, we reviewed publications in the English language traceable through Embase, MEDLINE, Web of Science Core Collection, Google Scholar, Coc-hrane Central, and PubMed with key-words including Type 2 diabetes, diab-etic nephropathy, osteoinductive fact-or, pathogenesis, and biomarkers. All relevant original research, case reports, metaanalysis, and systemic review arti-cles were considered.

Diabetes Mellitus

Diabetes mellitus is a metabolic dise-ase characterized by abnormalities in insulin secretion, insulin action, or bo-th leading to hyperglycemia. It's a chr-onic, non-communicable disease affe-cting multiple systems with pandemic proportions. Chronic hyperglycemia damages the micro- and macro-vascu-lature, eventually resulting in Diabetic nephronpathy, retinopathy, and neuro-pathhy, all of which have signific-ant consequences on quality of life and life expectancy. Endothelial dysfunc-tion is the source of this complex pathogennesis [14]. According to the WHO, DM of all types has increased dramatically throughout the world in recent decades. The number of patients with diabetes has risen from 108 million (4.7 percent) in 1980 to 425 million (8.5 percent) in 2017 and

is expected to reach 629 million by 2045. Diabetes, along with the expanding obesity crisis, has emerged as one of the most pressing and prevalent health problems in recent decades. DM is currently the 7th leading cause of death in the United States and worldwide[15]. Africa was said to have 16 million people with DM, 58 million in Europe, and 39 million in the Middle East and North Africa[16].

Type 2 Diabetes Mellitus

T2DM is the most common type of diabetes, accounting for 90–95 percent of all diagnosed cases worldwide[17]. It arises as a result of a gradual loss of β-cell insulin secretion, which typically occurs in the background of insulin resistance [18]. The etiology of T2DM appears to include a complex interplay between environmental and genetic elements. When a diabetic lifestyle (i.e., high-calorie intake, sedentary living with insufficient caloric expenditure, and obesity) is combined with a prone genotype, the illness is thought to emerge[19]. The body mass index at which the risk of T2DM increases differs by racial group. In this regard, Asian descent races are more likely to develop diabetes at lower levels of obesity. Hypertension, pre-hypertension, and diabetes are more common in white people than in African-Americans[19]. Furthermore, certain people may be prone to T2DM as a result of low birth weight. Infant weight has an indirect effect on insulin resistance in adulthood, mediated primarily by its effect on BMI and waist circumference [20]. Insulin resistance associated with metabolic syndrome triples the risk of coronary artery disease, myocardial infarction, stroke, and cardiovascular death [21]. Almost 90% of type 2 diabetic patients are obese, and obesity itself causes some degree of insulin resistance, particularly visceral fats[22]. Therefore, the management of obesity was recently proposed to be a primary goal for the control of T2DM[23]. However, a large population-based prospective study has found that an energy-dense diet may be a risk factor for the development of di-abetes independent of baseline obes-ity[24]. Pollutants in the environment may contribute to the growth and progression of T2DM[25]. The chance of getting T2DM rises with age, obesity, and a lack of physical activity. Women with previous gestational diabetes mellitus (GDM), hypertension or dyslipidemia, polycystic ovarian syndrome, and specific racial/ethnic subgroups are more likely to develop this disease. T2DM is more frequently associated with a substantial genetic susceptibility or family history in first-degree relatives than T1DM. T2DM genetics, on the other hand, is poorly understood[18].

Type 2 Diabetes and Insulin Resistance

Individuals with T2DM consistently display three cardinal abnormalities: 1) Insulin resistance in peripheral tissues, particularly muscle, fat, and the liver, 2) Inadequate insulin secretion, the release of aberrant insulin molecules, and/or inadequate proinsulin-to-insulin conversion, especially in response to glucose stimulation, and 3) Increased glucose production in the liver[26,27].

Insulin resistance manifests as an impaired response to endogenous or exogenous insulin in those who are prone to T2DM before hyperglycemia develops. Obesity, a sedentary lifestyle, pregnancy, and excess hormones are all factors that contribute to it[28,29]. Because the pancreas normally compensates by increasing the amount of insulin released, an elevated fasting insulin level is one indicator of insulin resistance[26]. Hyperinsulinemia is a risk factor for atherosclerosis and Coronary heart disease[29]. Circulating insulin is also antagonized by hormonal and non-hormonal effectors: a) Increased amounts of counter-regulating hormones (e.g., growth hormone, cortisol, glucagon, or catecholamine), b) Increased plasma free fatty acids, c) Anti-insulin antibodies, and, d) Inflammatory cytokines, e.g., TNF-α and IL-6. Insulin receptor and post-receptor defects produce a poor response at the target tissue[26]. Insulin resistance is a protective adaptive response of essential tissues, including the heart, against insulin-induced metabolic stress and the flooding energy influx[30]. A fundamental component of T2DM development and progression is the increaseing dysfunction of pancreatic islet cells due to continuous exposure to hyperglycemia and/or free fatty acid[31].

Complications of Diabetes Mellitus:

Hypoglycemia, hyperosmolar non-ketotic coma, lactic acidosis, and diabetic ketoacidosis are all acute consequences of T2DM[32,33]. Diabetic macroangiopathy, which includes cardiovascular problems, stroke, and peripheral vascular disease, is one of the chronic consequences[33]. Diabetic microangiopathy damages the retina, kidneys, and vasa nervosa's small blood arteries. This results in nephropathy, retinopathy, and neuropathy as pathognomonic characteristics of DM, all of which enhance the morbidity and mortality of those who are affected[18]. Furthermore, indices of subclinical inflammation, such as high C-reactive protein (CRP), are linked to the prevalence of T2DM and metabolic syndrome[34]. Also, in T2DM and its consequences, there is a strong link between inflammation, aging, and oxidative stress[35].

Diabetic Nephropathy

DN is one of the most devastating diabetic microangiopathies, and it has become a worldwide epidemic, accountting for around one-third of all ESRD cases[36,37]. An early sign of DN is albuminuria[38]. Recording two of three consecutive abnormal albumin values collected on different days is required for persistent abnormal albumin excretion. One of the main test confounders is the exercise within 24 hours, infection, fever, congestive heart failure, significant hyperglycemia, menstruation, and severe hypertension[39]. DN is marked by persistent albuminuria and progressive deterioration of renal function. It takes between 10 and 20 years to develop[40].

Global Prevalence and Burden of Diabetic Nephropathy*:*

DN is reported to occur in 20-50% of people with type 1 & 2 DM[41]. Unlike T1DM, DN leads to ESRD in a smaller percentage of T2DM patients[42]. DN accounts for around 40-50 percent of

all ESRD cases [43]. As a result, in many communities, DN is the most common cause of ESRD, followed by hypertension [44].

Stages and Natural History of Diabetic Nephropathy:

CKD typically occurs after 10 years of diabetes in T1DM, however, it may be present at the time of T2DM diagnosis[18]. The five stages of DN are as follows: 1) The early stage of hypertrophy, which is marked by an increase in renal plasma flow and glomerular filtration rate (GFR); 2) The silent stage, which is marked by morphological changes such as thickening of the glomerular basement membrane (GBM), glomerular hypertrophy, and tubulointerstitial expansion. 3) A developing DN that can be detected by microalbuminuria at the onset of hypertension. 4) Open DN, characterized by dipstick positive proteinuria, and 5) Finally uremia and ESRD[45]. Despite the fact that creatinine may appear normal for more than 15 years in patients with proteinuria, GFR rapidly diminishes without warning symptoms[46,47]. GBM thickening and mesangium expansion may occur before albuminuria or eGFR decrease and can be diagnosed 2-8 years after DM diagnosis[48]. Because T2DM can go unnoticed for years and worsen with poor glycemic management, more people with DN had it at the time of diagnosis[49]. About 2040% of microalbuminuric T2DM patients progress to macroalbuminuria, with 20% progressing to ESRD[42].

Risk Factors for Diabetic Nephropathy:

Diabetic microvascular complications and poor glycemic control are linked in a significant way [50]. On the other hand, proper blood sugar control can significantly minimize the risk of albuminuria developing or progressing[45]. Elevated blood pressure values are a common finding in patients with type 2 diabetes mellitus and are thought to reflect, at least in part, the impact of the underlying insulin resistance on the vasculature and kidney [51]. The most important cause of DN progression and the point of effective intervention is hypertension [52]. Every 10 mmHg drop in systolic blood pressure reduces the risk of microvascular problems by 13%, with the lowest risk among those patients with SBP <120 mmHg [53]. Dyslipidemia is a major risk factor for atherosclerosis, cardiovascular diseases, and DN[54,55]. Smoking has been believed to be a major risk factor for the development and progression of diabetic kidney disease. In T2DM patients, smokers had a higher prevalence of lower eGFR (60 mL/min/1.73 m2), microalbuminuria, and macroalbuminuria than non-smokers. Smokinginduced oxidative stress is thought to be the mechanism by which smoking affects the progression of DN by activating various cellular pathways[56]. The risk of getting DN has a hereditary component, which is likely polygenetic. The prevalence of DN varies by race and ethnicity. African Americans, Native Americans, and Mexican Americans are at a higher risk than European Am-ericans, possibly due to APOL1 gene variations. Even if access to care may be a factor in the disparity in preval-ence, it is unlikely to be the

only one, as it clusters in familial studies, as the Pima Indian community demonstrate-es[57]. The Family Investigation of Ne-phropathy and Diabetes (FIND) group discovered a strong link between DN and the chromosomal regions 10p15, 7q21.3, 18q22.3, and 14q23.1 [58]. The eGFR phenotype was found to have a strong connection with chromosome regions 18q23.3, 8q13.3, and 1q43[59], suggesting a link between chromosomes 7q, 3p 22q, and 16q and urine albumin excretion status in European-American and African-American populations [60].

Pathogenesis of Diabetic Nephropathy:

Multiple mechanisms contribute to the development and effects of DN, including metabolic and hemodynamic alterations caused by hyperglycemia, hypertension, and hereditary susceptibility, all of which prepare the stage for kidney injury[61]. Due to a disparity in efferent and afferent arteriole resistance, hydrostatic intraglomerular pressure and glomerular filtration rate increase[62]. Vasoactive hormones (e.g., endothelin and the renninangiotensinaldosterone system) and inflamematory cytokines may be secreted in response to DN hemodynamic abnormalities[63,64]. TGF-β1 and other profibrotic cytokines exacerbate hemodynamic abnormalities by raising intraglomerular and systemic pressure. The resistance in the glomeruli afferent arterioles is lower than the resistance in the efferent ones, resulting in glomerular hyperperfusion and higher intraglomerular pressure[64,65]. Several factors, including nitric oxide, vascular endothelial growth factor, and prostanoids, have been implicated in this defective autoregulation. Albumin loss occurs as a result of these early hemodynamic alterations, which include GBM thickening, podocyte damage, and mesangial cell matrix overproduction[66].

Changes in protein structure, induction of cellular stress effectors (e.g., Mitogen-activated protein kinase, NFB, and PKC), expression of growth factors and pro-inflammatory cytokines, Connective tissue growth factor (CTGF), and transforming growth factor (TGF)-, plasminogen activator inhibitor-1, and extracellular matrix are all caused by oxidative stress-induced non-enzymatic glycosylation of lipids [65,67,68]. All of these alterations are correlated to the stage of albuminuria. Platelet-derived growth factor (PDGF) expression is also increased in DN, and it regulates platelet aggregation, chemotaxis, and vascular tone through modulating platelet aggregation, chemotaxis, and vascular tone. Increased VEGF levels in the DN mediate angiogenesis, leukocyte trafficking, and vasodilation, and are linked to OGN expression[64,65,69,70].

Renal Pathology in Diabetic Nephropathy:

The histopathological lesions of DN have been classified into Class I) Nearnormal light microscopy and glomerular basement membrane thickness by electron microscopy (GBM >395 nm in females and >430 nm in males), Class IIa) Mild mesangial expansion in >25 percent of the observed mesangium, Class IIb) Severe mesangial expansion in >25 percent of the obse-

rved mesangium, Class III) Nodular sclerasis in at least one glomerulus, and, Class IV) advanced global glomerulosclerosis in >50% of glomeruli[41]. Renal pathological alterations are present in patients with long-term diabetes before microalbuminuria develops[71]. The typical light microscopic features of DN are made up of three major lesions: Thickened GBM and tubular basement membranes, diffuse mesangial expansion, and afferent and efferent arteriole hyalinosis are all symptoms of afferent and efferent arteriole hyalineosis. 1) Tubular atrophy, 2) Thickened tubular basement membrane, 3) Interstitial fibrosis and/or inflammation, and 4) Advanced arteriolar hyalinosis are all atypical lesions[72]. Another classification scheme divides diabetic changes into four levels of severity: 1) Class I includes only GBM thickening (>2 standard deviations from normal), 2) Class II includes mesangial enlargement (mild to severe), 3) Class III includes nodular sclerosis, and 4) Class IV includes advanced DN with all previous changes, as well as global sclerosis of >50 percent of glomeruli[73]. The existence of immunological complexes in DN was not confirmed by immunofluorescence (IF) microscopy. The kidneys of diabetes patients often show a characteristic pattern of linear homogenous IgG staining along the glomerular and tubular basement membranes, with no complement or deposits on electron microscopy (EM). This staining is also not believed to be symptomatic of immunological damage, but it could reflect the aberrant GBM's'stickiness' to IF antisera[73]. By EM, advanced DN displays a widespread thickening of the GBM lamina densa that is frequently more than twice normal. The basement membranes are frequently separated from the overlaying foot processes in podocytes, resulting in significant effacement of the foot processes. Mesangium has an expanded matrix, which is frequently filled with collagen fibrils. This matrix is interwoven with cell detritus and fragments of cell organelles. In glomeruli with mesangiolysis, there may be some disorder and fraying of the mesangium at the interface with the glomerular capillary lumen. Hyalinosis lesions have a coarsely granular, electron-dense appearance, and can be found in capsular droplets, sclerosis with hyalinosis, or dispersed throughout the mesangium and along the capillary walls. It can be difficult to distinguish non-immune hyaline accumulations from granular, electron-dense immune deposits. As a result, histological and IF findings must be carefully linked with the likelihood of superimposed immune complex-mediated glomerulonephritis. In both atrophic and intact tubules, the thickness of the tubular base-ment membrane increases. Tubular atr-ophy is proportional to interstitial fibr-osis. Hyalinosis of the afferent and eff-erent arterioles is a hallmark of DN, as opposed to other types of hyalinosis that solely affect the afferent arter-ioles[41]. Furthermore, severe arterio-sclerotic lesions in all caliber arteries are common, especially in T2DM pat-ients, who are often older than type 1 diabetics. The presence of many tiny arterioles-like vessels at the glomerular

vascular pole was identified by a three-dimensional examination of the arterioles, which indicated a complex arborization of the arterioles[74]. The findings of urine biomarkers in humans support the theory that tubular injury causes early DN to grow in a primary rather than a secondary manner[75].

Diagnosis of Diabetic Kidney Disease:

In the absence of signs or symptoms of other major causes of kidney impairment, diabetic kidney disease (DKD) is often diagnosed clinically based on albuminuria and/or decreased eGFR. Long-term diabetes, retinopathy, albuminuria without severe hematuria, and progressive decrease of eGFR are all documented symptoms of DKD. In T2DM, however, signs of CKD may be present at diagnosis with or without retinopathy, and a reduced eGFR without albuminuria has been recorded frequently in both T1DM and T2DM. Alternative or additional causes of kidney illness include active urinary sediment (including red or white blood ce-lls or cellular casts), rapidly increasing albuminuria or nephrotic syndrome, rapidly deteriorating eGFR, or lack of retinopathy (in T1DM)[18].

There is significant evidence that albuminuria screening should be performed in all diabetic patients. Urinary albumin-creatinine ratio (UACR mg/g) in a randomized spot urine collection is the most effective way to detect albuminuria. Timed or 24-hour collections are more difficult to manage and offer nothing to accuracy or prediction. The cost of measuring albumin alone in a spot urine sample (either by immunoassay or with a responsive albuminuria-specific dipstick test) without also measuring urine creatinine (Cr) is lower, but it is more prone to falsenegative and false-positive results due to variations in urine concentration due to hydration. The normal UACR is 30 mg/g, and high urine albumin excretion is indicated as 30 mg/g[76]. Albuminuria is typically divided into three categories: 1) Normoalbuminuria (UACR 30 mg/g; 24-hour urine albumin 30 mg), 2) Microalbuminuria (UACR 30–300 mg/g; 24-hour urine albumin 30-300 mg), and 3) Macroalbuminuria (UACR 300 mg/g; 24-hour urine albumin > 300 mg)[77].

The estimated GFR (eGFR) of serum creatinine should be measured using a validated formula, most generally the 4-variable MDRD equation [GFR in mL/min/1.73 m^2 = 175 × $(_{SCR})^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if female) × (1.212 if African American)] as it provides reasonably accurate GFR estimates in patients with CKD. The equation estimates GFR based on sex, race, and age through the use of endogenous creat-inine clearance[78,79]. eGFR persistently lower than 60 mL/min/1.73 m^2 is regarded as abnormal, although, optimal thresholds for clinical diagnosis are debated in older adults[18].

Another biomarker in DN patients is immunoglobulin excretion in the urine. IgM is the most common human antibody, and its excretion indicates a ma-jor problem with the glomerular cap-llary wall. According to a recent study, patients with greater IgM excretion in urine had a 4.9-fold higher risk of renal failure. This implies that

regardless of the level of albuminuria, higher IgM urine excretion was a predictor of renal impairment[80]. Type IV collagen is the main component secreted from the glomerular and tubular basement membranes, as well as the mesangial matrix. Urine type IV collagen was more resistant than urinary albumin as a m-rker for early DN[81]. Podocytes are the principal structural components of the glomerular filtration barrier. They may provide potential urine indicators for early DN diagnosis[82]. The American Diabetes Association and the National Kidney Foundation recommend that all patients with diabetes have their serum creatinine levels checked (to determine their GFR). The most sensitive and exact DN marker for tracking and monitoring the course of renal damage is serum cystatin-C.[83]. Renal biopsy is recommended when there is a rapid onset of proteinuria (regardless of whether it progresses from microalbuminuria to macroalbuminuria), no retinopathy, active urinary sediment, hematuria, or a possibility of other systemic disease-related nephropathies[84]. There could be a potential for kidney biopsy to be proven as a gold standard for DN diagnosis[85]. Diagnostic imaging technology has advanced to the point where clinicians can use it to help them make routine judgments about which patients they should biopsy to confirm DN. To identify DN from nondiabetic renal disorders (NDRD), interlobular renal artery echo-color-Doppler sampling and evaluation of intra-renal resistance indices (RI) were devised[86]. RI aids in the calculation of hemodynamic changes in the renal arteries. These are commonly found in DN patients due to changes in vascular compliance, which affect blood flow. As a result, renal Doppler can detect early alterations in blood flow and so indic-ate the onset of DN[87]. A RI of greater than 0.70 indicates that nephropathy will develop to ESRD, whereas a RI of less than 0.70 indicates that renal disease will progress slowly[88].

Osteoglycin/Osteoinductive Factor

Extracellular matrix (ECM) proteoglycans (PGs) have been identified as collagenous network organizers as well as molecules with cell signaling capabilities, regulating cellular development, differentiation, and migration. Small leucine-rich proteoglycans (SERPs) are a fast-increasing subfamily of extracellular PGs generated by vascular smooth muscle cells, with 13 members encoded by distinct genes[70,89]. SERPs modulate numerous biological processes, including cell proliferation and differentiation, inflammation and fibrosis, and modulation of secretion and action of several growth factors through bo-th structural and nonstructural functi-ons - within the vascular extracellular matrix, in addition to bone, cartilage, and myocytes matrix[69,90]. The core domain of osteoglycin (OGN), a class III SLRP, is characterized by leucinerich repeats with numerous glycosylation sites, and the human OGN gene is localized at 9q22. It's found in the vascular matrix outside of cells[91,92]. The monogenic OGN is found in considerable levels in the cornea, aorta, sclera, skin, cartilage, and vagus nerve, as well as in smaller amounts in the cerebellum, kidney,

intestines, myocardium, and skeletal muscle. Mimecan is a secretory 34-kDa full-length protein encoded by the OGN gene. It is released as two C-terminal mature proteins with molecular weights of 25 and 12 kDa into human serum[93]. Osteoinductive Factor (OIF) was the initial name for the 12 kDa protein, which was later renamed to OGN. In many tissues, OGN possesses a tissue-specific glycosylation site as well as a variety of post-translational modifications[69]. OGN's 12-kDa product is produced in human pituitary corticotro-ph cells, where it promotes ACTH secretion, and glucocorticoids up-regulate it. It is derived from adipose tissue and acts as a satiety hormone in the hypothalamus, utilizing interleukin (IL)-1 and IL-6 without relying on leptin signaling [31,94-97]. Through diurnal rhythmic increases in corticosterone release by adrenal cells, OGN plays a part in the homeostatic responses to stress. Hypoglycemia and stress greatly reduce OGN expression in adrenal tissues, and ACTH has a similar effect[95].

The high conservation of OGN among organisms suggests that it has important physiological roles. This includes osteoclast and osteoclast-like cell suppression, heterotopic bone formation, a role in arthrodesis, and possible vascular matrix constituent functions[98]. OGN enhances T-lymphocyte recruitment[95]. OGN binds to bone morphogenetic proteins (BMPs), which are members of the transforming growth factor β (TGF-β) superfamily, and regulates their bioavailability and effects, such as promotion of osteoblastic cell proliferation and alkaline phosphatase activity in bone marrow stromal cells [5,89]. Through the effects of bone orthogenetic protein-2 and bone orthogenetic protein-3, OGN stimulates growth [99]. OGN also has a role in a number of pathologic conditions, including cardiovascular disease, cancer, and eye disease[69], preterm delivery [100], and tumor biology[95,98,101]. OGN is a very promising possibility for the development of novel therapeutic and/or biomarker techniques because of its enormous structural and functional diversity in normal physiology and pathological situations[69]. According to recent studies, OGN may play a role in the pathogenesis of DN. As a result, serum OGN could be used as a diagnostic marker for DN in its early stages[13]. It's also reasonable to think of it as a sensitive marker for detecting ea-rly microalbuminuria[9,12].

The key roles of OGN include osteoclast and osteoclast-like cell inhibition, heterotopic bone induction, and possible vascular matrix functions[102]. OGN is an important regulator of cell development, differentiation, and proliferation[98]. OGN co-expresses in the pituitary and associates with adren-ocorticotropic hormone (ACTH) as well as the adrenal cortex, maintaining the hypothalamic-pituitary-adrenal axis' responsibilities in balance[93,96]. OGN is also a component of the normal vascular matrix, and it is abundantly expressed in differentiated cardiomyocytes, cardiac fibroblasts, and vascular smooth muscle cells (VSMCs), but it is downregulated in vitro proliferated VSMCs. As a result, OGN could be a

potential VSMC differentiating marker[103-105]. As a result, OGN plays a critical role in capillary regulation [106]. OGN plays a role in metabolism. It regulates the metabolism of lipids, carbohydrates, and energy[106]. Given OGN's high structural and functional diversity, as well as its widespread expression, it's no surprise that it's important in a wide range of disorders, including eye, bone, heart, vasculature, neurologic disease, kidney disease, and cancer[69]. OGN has been found as a potential biomarker for a variety of disorders in several investigations. Arrays, mass spectrometry, ELISA, and other high-throughput screening technologies are used in the majority of these studies. OGN was identified as a possible biomarker in amniotic fluids in research to identify women at risk of preterm labor and delivery[100]. In blood, OGN was likewise found to be a direct cleavage result of ADAM17. ADAM17 is in charge of releasing the soluble form of a number of cell-surface proteins, the majority of which are linked to pathologic conditions such as hypertension, inflammation, connective tissue disease, and cancer[69,70,107]. Circulating OGN levels have been linked to major adverse cardiovascular events in patients who had coronary angiography for acute coronary syndrome or stable angina pectoris over a one-year period, and the direction of change in circulating OGN levels pred-icts left ventricular remodeling in heart failure patients[108]. OGN overexpresssion, on the other hand, decreases proliferation and invasion in human cancer cell lines, reverses epithelial-to-mesenchymal transition via repression of the PI3K-/Akt/mTOR pathway, and is associated with poor prognosis and survival when compared to normal tissues. This sparked interest in OGN's potential as a tumor suppressor gene [95,109,110]. In response to ER stress, the shortened version of C/EBP promotes cell death by activating MAPKs and boosting OGN expression. P53 and UV irradiation both promote OGN expression, as UV causes ER stress[111].

OGN and Vascular Health

Vascular smooth muscle cells, cardiomyocytes, and cardiac fibroblasts, but not endothelial cells or macrophages, express OGN, which is a component of the vascular extracellular matrix. OGN knockout mice experienced diastolic dysfunction as a result of cardiac fibrosis, but OGN was not associated with calcification in atherosclerotic or carotid plaques[112]. In coronary angiography patients, however, circulating OGN levels were associated with a higher risk of significant cardiovascular events[105]. In a Korean prospective cohort of non-diabetic patients with chronic kidney disease only, OGN level was found to be a predictor of all-cause mortality, cardiovascular, and cerebrovascular events, and it correlated positively with CRP and negatively with proteinuria and hemoglobin content, but not with eGFR[113]. The expression of OGN in aortic tissues from aortic dissection patients is considerably lower than in healthy controls. The activation of VEGF signaling (VEGFR, AKT, and ER K1/2) increased VEGF-induced cellular proliferation and migration in rats with OGN knockdown in aortic

smooth muscle cells[11]. When the level of OGN mRNA expression in these rat aortic smooth muscle cells was lowered by treatment with basic fibroblast growth factor, TGF, PDGF, and angiotensin II, similar effects were observed[103]. Competitive inhibitory binding of OGN to VEGFR2 was discovered in human umbilical vein endothelial cells, which negatively modulates its downstream signaling pathways[10]. In these cells, the Knockdown of OGN increases phosphorylation of AKT and ER K1/2 in response to VEGF[114]. OGN depletion nhibits epithelial/endothelialmesenchymal transition, and myocardial fibroblast proliferation, and causes apoptosis in myocarditis[115].

OGN & Diabetes

1,25-dihydroxy-cholecalciferol (calcitriol), an antidiabetic, insulin secretion and sensitizer, stimulates the expression of the OGN gene in myoblast. Furthermore, a lack of vitamin D hormone exacerbates diabetes-induced muscle wasting by lowering OGN expression. This hormone reverses the suppression of OGN expression in myoblastic cells caused by advanced glycation end products[106,116,117]. Loss of the OGN gene impairs glucose tolerance and induces diet-independent white adipose buildup. Furthermore, during an insulin tolerance test in mice, OGN treatment decreases blood glucose and enhances glucose elimination in a dose-dependent manner[118]. The expression of OGN was discovered to be higher in visceral adipose tissue of overweight human participants than in subcutaneous white adipose tissue[119]. In postmenopausal women, the circulating level of OGN had a significant connection with the duration of T2DM illness[120]. Although bariatric gastric surgery has been shown to produce metabolic benefits in addition to weight loss, the causes are unknown. A change in OGN level, which correlates negatively with BMI and positively with lean body mass, modulates whole-body energy supplies by altering glucose uptake through changes in insulin secretion and sensitivity, and altering food intake through central signaling, according to one of the proposed mechanisms. Glucose tolerance is decreased in OGN knockout mi-ce, and insulin levels are raised, leadi-ng to an increase in white adipose tiss-ue in animals fed a conventional or hi-gh-fat diet. In vitro, OGN administrati-on increases the expression of Ins1 and Ins2 mRNA as well as insulin secretion in a dose-dependent manner[118,121]. In T1DM and T2DM patients with HbA1c of ≥65 mmol, serum OGN levels correlated positively with BMI but not with glycemic control or metabolic biomarkers[122]. Osterix, a transcription regulator, induces OGN expression, which may be involved in its ability to inhibit adipogenesis by superssing the expression of adipogenic markers such as CCAAT/enhancerbinding protein alpha (C/EBPα) and inhibiting the transcription function of peroxisome proliferator-activated receptor-gamma (PPARγ)[123]. The agedependent variations in circulating OGN and their relationnship with glucose energy metabolism demonstrated a highly significant positive link with aerobic capacity (higher VO2 peak), especially in those

under 50 years old, and with higher circulating glucose levels but not insulin resistance. Over the course of his life, OGN had a U-shaped curve[124].

OGN and Diabetic Nephropathy

Biglycan, decorin, and osteoglycin are small leucine-rich repeat proteoglycans that modulate vascular extracellular matrix[125-127]. When DN participants were compared to healthy controls and T2DM patients, serum OGN levels were considerably higher. As a result, in people with T2DM, OGN could be a sign of early-stage DN[9]. Angiogenesis and atherosclerosis are both enhanced by OGN. OGN is common in the normal vasculature as well as in Atherosclerotic and restenotic artery lesionns[127]. Vascular endothelial dysfunction and atherosclerosis of the renal arteries are important factors in the etiology and progression of DN[102]. This effect has been attributed to OGN by its association with TGF-like bone morphogenetic proteins[69]. TGF-1 promotes glomerulosclerosis, interstitial fibrosis, and the reduction of GFR in DM by increasing urine excretion of albumin, water, electrolytes, and glucose, as well as boosting glomerulusclerosis, interstitial fibrosis, and glucose excretion. TGF-1 promotes the accumulation of extracellular matrix in DN. TGF signaling is important for the accumulation of ECM in DN[128]. Because glucose availability is diminished in diabetes, the metabolic shift from glycolysis to oxidative phosphorrylation happens by utilizing more fatty acids as an energy source. As a result, the mitochondrial electron transport chain increases superoxide generation and triggers three major hyperglycemic damage pathways[129]. According to one study, OGN is one of the most fundamental capillary chemicals and plays a critical function in capillary health. The lung, skeletal muscle, testis, and adipose tissue all had sufficient quantities of OGN mRNA[106]. Serum OGN has been demonstrated to be released by vulnerable hemorrhagic carotid and coron-ary atherosclerotic plaques, and it may have prognostic value in individuals with coronary artery disease. It regulat-es capillary regeneration and permeabi-lity by suppressing epithelial-mesench-ymal and endothelial-mesenchymal transitions, as well as TGF-β1, EGF receptor/Akt, and vascular endothelial growth factor (VEGF) signaling [70,95,105].

A recent study has discovered that OGN has a role in angiogenesis and atherosclerosis development, and it is well understood that vascular endothelial damage and renal artery atherosclerosis are significant factors in the pathogenesis and progression of DN [70,105]. Higher circulating OGN concentrations in CAD patients have previously been shown to have prognostic value[105]. OGN has a function in heart failure patients, as evidenced by its clear correlation to a history of MI, as well as inflammation and fibrosis biomarkers[130]. The use of serum OGN levels to detect diabetic osteopenia or osteoporosis has high diagnostic power. When OGN-expressing MC38 cells were incorporated into Matrigel plugs, they produced fewer blood vessels than control cells.

This indicates that OGN suppresses angiogenesis [9]. Furthermore, overexpression of OGN in MC38 cells reduced VEGF transcriptional activation induced by hypoxiainducible factor (HIF)-1α [70,95,10]. Proangiogenic factors, on the other hand, suppress OGN expression[70,103].

Studies on the use of OGN in predicting microalbuminuria and DN in the early stages are few and conflicting. González-Salvatierra et al. (2021) found that serum levels of OGN, as measured by an immunoassay, are considerably higher in T2DM patients compared to healthy controls in a crosssectional investigation. Such an increase was gradual and independently predicted the probability of mild incipient renal dysfunction in these patients, corresponding with the severity of kidney impairment[12]. Although the immunoassays serum OIF levels of healthy controls and T2DM patients were not substantially different, patients with DN had significantly greater levels than these two groups. Serum OIF levels had a positive association with serum creatinine and urea, but a negative relationship with eGFR, with excellent sensitivity and specificity for diagnosing early microalbuminuria, and even better for detecting macroalbuminuria and damage progression[13]. A third study discovered that the rate of microalbuminuria is negatively linked with OIF, which predicts microalbuminuria independently (102). Serum OGN levels are highly correlated with microalbuminuria and are low in stage 1 CKD, increasing to stage 3b with disease progression, then decreasing in stages 4 and 5[131]. Through activated epidermal growth factor receptor signaling, angiotensin II upregulates OGN expression in the mouse heart, reducing cardiac interstitial fibrosis, cardiac dysfunction, and cardiac myofibroblast proliferative and migratory activity[132]. In patients who had coronary angiography for acute coronary syndrome or stable angina pectoris, changes in serum OGN levels of individuals with susceptible atherosclerotic plaques independently predicted severe adverse cardiovascular events. As a result, OGN has the potential to be a useful biomarker for unfavorable cardiovascular events[105]. In atherosclerotic plaques, OGN expression is decreased[133,134]. By regulating the proliferation, death, and migration of vascular smooth muscle cells, OGN plays a role in the development of atherosclerosis. OGN content increases in the activated endothelium and thickened neointima with the progression of coronary atherosclerosis plaques, compared to the lipidosis and fibrosis stage and unstable plaques, at the advanced stage of fibrosis and calcification[135,136]. OGN levels in hypertension patients are higher than in healthy controls, and they are linked to increased arterial stiffness. Furthermore, in those patients, OGN, endothelin 1, creatinine, and diastolic blood pressure were all independent predictors of arterial stiffness[135]. Microalbuminuric and macroalbuminuric T1DM patients had significantly higher blood levels of OGN than healthy controls and normoalbuminuric T1DM patients, with significant positive correlations

with disease duration, creatinine, and urinary albumin-creatinine ratio, but significant negative correlations with eGFR and diabetes onset[137]. Working on T2DM patients, we found that the OGN concentration of OIF was significantly higher in microalbuminuric and macroalbuminuric T2DM patients than in normoalbuminuric patients and healthy control groups, and was significantly positively correlated with DM duration, creatinine, and UACR but significantly negatively correlated with eGFR. Increases in OGN levels were seen in the early stages of diabetic nephropathy in T2DM, even before the emergence of microalbuminuria, and increased as the diabetic nephropathy progressed[138].

Conclusion:

DN is a chronic diabetic kidney disease that occurs as a complication of longterm and poorly managed diabetes mellitus and is considered the main cause of ESRD. Chronic hyperglycemia-induced oxidative stress enhances dyslipidemia, production of pro-fibrogenic growth factors, proinflammatory, vascular damage, advanced glycation endproducts, and hemodynamic changes involved in glomerular sclerosis and interstitial tubular fibrosis. Persistent urinary albumin excretion, microalbuminuria, and macroalbuminuria are not only an internationally accepted standard for early clinical detection of DN, but in itself, chronic albuminuria is pathogenetic as it is harmful to renal tubular cells, causing tubular inflammation and fibrosis. DKD is characterized by chronic albuminuria and increased serum creatinine with a gradual decrease in eGFR. Unfortunately, this standard is easily affected by the heterogeneity of the clinical presentation, excretion, urinary tract infection, hypertension, heart failure, serious fever, and many other factors. Up to 3% of those with T2DM have already dev-eloped albuminuria at the time of diagnosis. Because of these issues, mi-croalbuminuria cannot fully explain whether patients are at risk of de-veloping DN or not. Therefore, the search for a more sensitive marker to predict DN in order to help us scan for DN at an earlier stage is still in the race. OGN/OIF was one of the biomarkers hoped to show higher specificity and sensitivity as an early predictor of DN and its progression. OGN is a component of the vascular wall and plays a vital role in its health and disease through modulating the expression of and signaling from several growth factors and cytokines and controlling cellular growth, proliferation and differentiation. The few published studies reported a promising negative correlation with the early deterioration in kidney function studies characterized by high specificity and sensitivity. Larger multicentric longitu-dinal studies are required to further the characterization of OGN as a promising biomarker/effector molecule in DN.

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