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Impact of Diabetes on Other Organs — Specifically the Heart, Eyes, and Kidneys

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ABSTRACT
Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia that exerts widespread systemic effects, leading to significant morbidity and mortality. Among its most critical complications are those affecting the heart, eyes, and kidneys. Chronic hyperglycemia promotes the formation of advanced glycation end-products (AGEs) and triggers oxidative stress and inflammation, which together drive vascular damage across organ systems. In the cardiovascular system, these processes result in endothelial dysfunction, accelerated atherosclerosis, coronary artery disease, and ultimately heart failure. Diabetic retinopathy is a leading cause of blindness worldwide, marked by microvascular changes including capillary leakage, neovascularization, and retinal ischemia. In the kidneys, hyperglycemia induces glomerular hyperfiltration, thickening of the basement membrane, and mesangial expansion, culminating in diabetic nephropathy—a major cause of end-stage renal disease. Understanding these pathophysiological mechanisms is essential for developing targeted therapeutic strategies and for implementing effective screening and prevention programs to reduce the burden of diabetes-related complications.

Keywords: Diabetes mellitus**,** Hyperglycemia**,** Advanced glycation end-products (AGEs)**,** Oxidative stress**,** Inflammation**,** Cardiovascular complications**,** Endothelial dysfunction**,** Diabetic retinopathy**,** Diabetic nephropathy**,** Microvascular damage**,** Atherosclerosis**,** Chronic kidney disease**,** Targeted therapy**,** Screening and prevention

I. INTRODUCTION

Diabetes mellitus, a chronic metabolic disorder characterized by elevated blood glucose levels, significantly impacts various organs beyond its primary effect on insulin regulation. Among the most vulnerable systems are the heart, eyes, and kidneys, which often suffer long-term damage due to prolonged hyperglycemia and associated metabolic disturbances. Cardiovascular complications remain the leading cause of morbidity and mortality in diabetic patients, with increased risks of coronary artery disease, heart failure, and stroke. The eyes are equally susceptible, as diabetes can lead to diabetic retinopathy—an irreversible condition that may cause blindness if untreated. Additionally, the kidneys are frequently affected, with diabetic nephropathy being a major cause of end-stage renal disease worldwide. Understanding these organ-specific complications is crucial for early detection, effective management, and reducing the overall burden of diabetes.

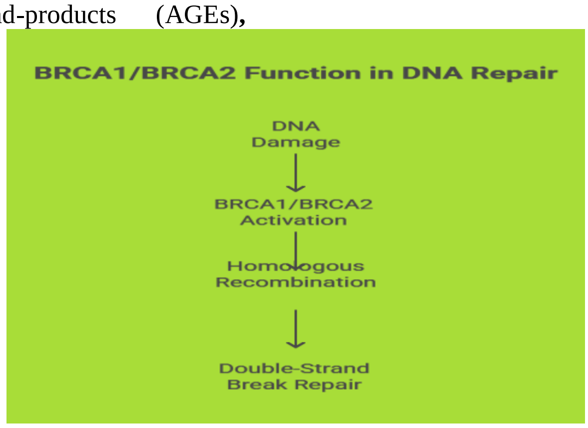

Fig.1. Schematic Diagram of BRCA1/BRCA2 Function in DNA Repair

1. HbA1c (Glycated Haemoglobin) – Long-Term Blood Sugar Control and Its Role in Cardiovascular Risk

HbA1c, or glycated haemoglobin, is one of the most critical biomarkers in diabetes management and cardiovascular risk assessment. It is formed when glucose in the blood binds irreversibly to the haemoglobin molecule in red blood cells. Since red blood cells have an average lifespan of around 120 days, HbA1c levels reflect the mean blood glucose concentration over the preceding two to three months, offering a reliable index of chronic glycaemic control.

In individuals with diabetes, consistently high HbA1c levels (≥6.5%) not only indicate poor blood sugar control but also serve as a predictor of vascular complications, especially cardiovascular disease (CVD). Hyperglycaemia leads to endothelial dysfunction, increased production of reactive oxygen species (ROS), and activation of inflammatory pathways—all of which contribute to atherogenesis. Studies like the UKPDS (United Kingdom Prospective Diabetes Study) have established a strong correlation between higher HbA1c levels and increased risk of myocardial infarction, stroke, and overall cardiovascular mortality.

Moreover, elevated HbA1c is associated with impaired nitric oxide production, promoting vasoconstriction and thrombosis. It also enhances the glycation of low-density lipoproteins (LDL), making them more atherogenic. Clinically, reducing HbA1c by just 1% has been shown to significantly reduce the risk of heart attacks by up to 14%, reinforcing its importance as both a diagnostic and prognostic tool in cardiovascular care.

Therefore, monitoring and maintaining HbA1c within a target range (usually <7% for most patients) is not only essential for glycaemic management but also a frontline strategy for reducing cardiovascular complications in diabetes.

2. LDL-C (Low-Density Lipoprotein Cholesterol) – The Atherogenic Risk Factor in Diabetic Cardiovascular Disease

LDL-C, or low-density lipoprotein cholesterol, is a primary carrier of cholesterol in the bloodstream and is often labelled as "bad cholesterol" due to its direct involvement in the formation of atherosclerotic plaques. In diabetic individuals, elevated LDL-C is one of the most significant contributors to cardiovascular disease (CVD), particularly coronary artery disease (CAD), heart attacks, and strokes.

What makes LDL-C more dangerous in diabetes is the alteration in its physical and biochemical properties. Diabetes is associated with increased production of small, dense LDL particles, which are more atherogenic than larger LDL particles because they can more easily penetrate the endothelium and are more prone to oxidative modification. Once oxidized, LDL-C becomes a key trigger for endothelial dysfunction and inflammation, initiating a cascade that results in plaque formation and arterial narrowing.

Furthermore, chronic hyperglycaemia promotes non-enzymatic glycation of LDL particles, impairing their clearance and enhancing their uptake by macrophages, which form foam cells—the building blocks of fatty streaks in early atherosclerosis. Elevated LDL-C also activates pro-inflammatory cytokines, adhesion molecules, and promotes smooth muscle proliferation in vessel walls.

From a clinical standpoint, LDL-C is a central target in lipid-lowering therapies. Guidelines often recommend stricter LDL-C targets (<70 mg/dL or even <55 mg/dL in high-risk diabetic patients) because reducing LDL-C substantially decreases the risk of cardiovascular events. Statins, the most commonly used LDL-lowering drugs, have shown clear benefits in both primary and secondary prevention of cardiovascular events in diabetic populations.

In conclusion, LDL-C plays a central mechanistic role in the development of cardiovascular complications in diabetes, and its control is critical to reducing atherogenic burden and improving long-term cardiovascular outcomes.

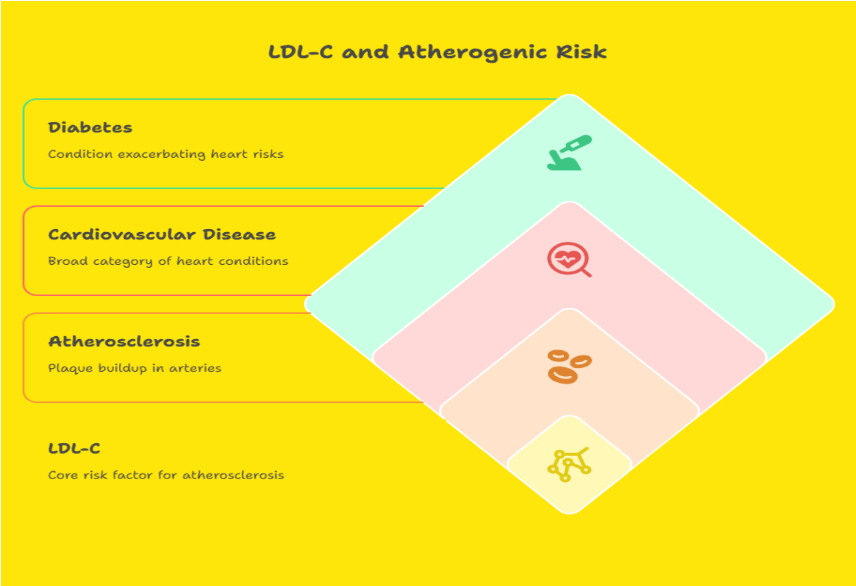

Fig.2. LDL-C (Low-Density Lipoprotein Cholesterol) – The Atherogenic Risk Factor in Diabetic Cardiovascular Disease

3. HDL-C (High-Density Lipoprotein Cholesterol) – The Protective Cholesterol Diminished in Diabetes

HDL-C, or high-density lipoprotein cholesterol, is commonly referred to as "good cholesterol" due to its protective role in cardiovascular health. Unlike LDL-C, which transports cholesterol to peripheral tissues, HDL-C is responsible for reverse cholesterol transport—carrying excess cholesterol away from arteries and back to the liver for excretion or recycling. This mechanism helps to prevent the buildup of cholesterol-rich atherosclerotic plaques within blood vessels.

In individuals with diabetes, HDL-C levels are typically reduced, and more importantly, the functionality of HDL particles is often impaired. Hyperglycaemia and insulin resistance contribute to alterations in HDL composition, such as decreased levels of apolipoprotein A-I (ApoA-I), the main protein component of HDL. Furthermore, the glycation and oxidation of HDL particles in the diabetic state reduce their antioxidant, anti-inflammatory, and vasodilatory properties, all of which are essential in maintaining endothelial integrity.

Low HDL-C levels (<40 mg/dL in men and <50 mg/dL in women) are independently associated with a higher risk of cardiovascular events in diabetic populations, particularly when combined with high LDL-C and triglyceride levels—a pattern known as atherogenic dyslipidemia. This triad significantly accelerates the progression of atherosclerosis, especially in the coronary and peripheral arteries.

Although raising HDL-C levels pharmacologically has not consistently translated into reduced cardiovascular events, lifestyle interventions such as weight loss, physical activity, and glycaemic control have shown modest improvements in HDL-C concentration and function. Additionally, HDL-C remains a valuable biomarker in assessing overall lipid risk profiles in diabetic patients.

In summary, HDL-C plays a crucial role in vascular protection, and its quantitative and qualitative decline in diabetes contributes meaningfully to increased cardiovascular risk.

4. Triglycerides – The Hidden Atherogenic Risk in Insulin Resistance and Diabetes

Triglycerides are a form of fat (lipid) stored in fat cells and used for energy between meals. In the context of diabetes—especially type 2—triglyceride levels are often elevated due to insulin resistance, which disrupts normal lipid metabolism. This elevation is a hallmark of diabetic dyslipidaemia, commonly characterized by high triglycerides, low HDL-C, and small dense LDL particles, all of which contribute synergistically to atherogenesis.

Under normal metabolic conditions, insulin inhibits the release of free fatty acids from adipose tissue and suppresses hepatic very-low-

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density lipoprotein (VLDL) production. However, in insulin resistance, this regulatory mechanism is impaired. As a result, the liver releases excessive VLDL particles, which are rich in triglycerides. These particles interact with cholesterol-rich HDL and LDL via the enzyme cholesteryl ester transfer protein (CETP), leading to HDL depletion and the formation of small dense LDL particles—both of which are highly atherogenic.

Elevated triglyceride levels (>150 mg/dL) are independently associated with increased risk of coronary artery disease, myocardial infarction, and pancreatitis. Moreover, high postprandial triglyceride levels—common in diabetics—are linked to endothelial dysfunction, oxidative stress, and low-grade inflammation, all of which accelerate vascular damage.

Although triglycerides were once considered a secondary target in lipid management, recent evidence emphasizes their significance in diabetic cardiovascular risk. Treatment strategies include lifestyle modification (diet, weight loss, physical activity), optimal glycaemic control, and pharmacologic agents such as fibrates, omega-3 fatty acids, and in some cases, statins.

In conclusion, triglycerides are not just passive storage fats—they are active participants in vascular pathology in diabetes, and their elevation reflects deeper metabolic dysfunction that must be addressed to prevent cardiovascular events.

5. CRP (C-Reactive Protein) – A Marker of Inflammation and Silent Cardiovascular Risk in Diabetes

C-reactive protein (CRP) is an acute-phase protein synthesized by the liver in response to inflammation, particularly triggered by cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). In diabetes, particularly type 2, there is a state of chronic low-grade systemic inflammation, and CRP—especially high-sensitivity CRP (hs-CRP)—has emerged as a powerful independent predictor of cardiovascular events.

Elevated hs-CRP levels in diabetic patients are associated with endothelial dysfunction, plaque instability, and thrombosis, all of which contribute to an increased risk of atherosclerosis, myocardial infarction, and stroke. What makes CRP clinically valuable is that it can detect vascular inflammation even before structural heart disease becomes apparent, making it a prognostic marker for subclinical cardiovascular disease.

Diabetes itself promotes the secretion of inflammatory mediators via mechanisms such as oxidative stress, advanced glycation end-products (AGEs), and adipose tissue-derived cytokines. This pro-inflammatory environment stimulates CRP production, and elevated levels (>2 mg/L) have been strongly linked to poor cardiovascular outcomes, even in individuals with otherwise normal lipid profiles.

Importantly, the predictive power of CRP adds value beyond traditional lipid measurements. The JUPITER trial demonstrated that individuals with normal LDL-C but elevated hs-CRP significantly benefited from statin therapy, which lowered both LDL and CRP levels, reducing cardiovascular events.

CRP is not only a marker but also plays a causative role in atherogenesis by promoting monocyte adhesion, endothelial dysfunction, and smooth muscle cell proliferation. Thus, elevated CRP levels should prompt aggressive intervention—not just for inflammation, but also for glycemic and lipid management.

In summary, CRP bridges the gap between metabolic dysregulation and cardiovascular risk in diabetes. Its inclusion in cardiovascular risk profiling allows for earlier detection, better prevention, and more personalized management of diabetic heart disease.

6. NT-proBNP (N-terminal pro-B-type Natriuretic Peptide) – Early Indicator of Heart Failure in Diabetic Patients

NT-proBNP is a biomarker released primarily by the cardiac ventricles in response to increased wall stress, such as volume overload or elevated intracardiac pressure. It is a fragment of the precursor proBNP, which is cleaved into biologically active BNP and inactive NT-proBNP. While both forms are clinically useful, NT-proBNP has a longer half-life and greater stability in circulation, making it a preferred marker in diagnosing and monitoring heart failure (HF).

In the context of diabetes, especially in patients with type 2 diabetes and long-standing hyperglycemia, the risk of developing heart failure—particularly heart failure with preserved ejection fraction (HFpEF)—is substantially elevated. Diabetic cardiomyopathy, characterized by myocardial fibrosis, stiffness, and impaired relaxation, can occur independently of ischemic heart disease. In such conditions, NT-proBNP levels often rise even before overt symptoms appear, making it a valuable early indicator of subclinical ventricular dysfunction.

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NT-proBNP is also useful for distinguishing between cardiac and non-cardiac causes of dyspnea in diabetic individuals, a population in which comorbidities such as obesity, chronic kidney disease, and autonomic neuropathy can mask typical heart failure signs. Moreover, higher NT-proBNP levels have strong prognostic implications, predicting not only mortality and hospital readmission rates in heart failure but also cardiovascular events in asymptomatic diabetic individuals.

Importantly, NT-proBNP concentrations must be interpreted in context—renal impairment, which is common in diabetes, can independently elevate its levels due to reduced clearance. Nonetheless, it remains a cornerstone in guiding therapeutic decisions, including the need for echocardiography, medication adjustments, or hospitalization.

In conclusion, NT-proBNP serves as a sensitive and specific biomarker for identifying early heart failure and assessing cardiovascular risk in diabetes. Its role extends beyond diagnosis to prognosis and management, making it essential in the comprehensive

7. Troponin – Silent Cardiac Injury Marker in Diabetes

Cardiac troponins—primarily Troponin I (cTnI) and Troponin T (cTnT)—are highly specific and sensitive biomarkers for myocardial injury. These regulatory proteins are released into the bloodstream when cardiac muscle cells are damaged, making them the gold standard for diagnosing acute myocardial infarction (AMI). In individuals with diabetes, troponin levels carry both diagnostic and prognostic significance, often revealing silent or subclinical myocardial damage.

Diabetes increases the risk of both macrovascular (e.g., coronary artery disease) and microvascular complications that can lead to ischemia and cardiomyocyte injury, even in the absence of overt symptoms. Many diabetic patients experience "silent" heart attacks, owing to autonomic neuropathy, which blunts typical chest pain perception. Elevated troponin levels in such patients can be the only early sign of cardiac distress and should prompt immediate evaluation.

Moreover, high-sensitivity troponin assays (hs-cTnI and hs-cTnT) now allow detection of even minimal myocardial injury. Chronically elevated troponin levels, even below the threshold for AMI, are associated with increased cardiovascular mortality, left ventricular dysfunction, and heart failure risk in diabetic populations. This has important implications for risk stratification and long-term cardiac care, especially since diabetic individuals are often underdiagnosed or undertreated for cardiac issues.

Pathophysiologically, chronic hyperglycemia contributes to oxidative stress, microvascular ischemia, endothelial damage, and inflammation, all of which can cause low-grade, ongoing myocardial injury detectable via troponin. Additionally, conditions frequently coexisting with diabetes—such as hypertension, chronic kidney disease, and left ventricular hypertrophy—can exacerbate myocardial strain, further elevating troponin levels.

In clinical settings, even mildly elevated troponin in a diabetic patient without chest pain should never be dismissed. It may reflect underlying diabetic cardiomyopathy, chronic ischemia, or even early-stage heart failure, necessitating further investigation with echocardiography, stress testing, or coronary imaging.

In summary, troponin is not just a marker for acute coronary syndromes in diabetes—it is a window into chronic cardiac health, enabling early intervention in a population at high risk for undetected myocardial damage.

8. ECG Abnormalities – Non-Invasive Clues to Silent Cardiovascular Disease in Diabetes

While not a biochemical biomarker, electrocardiography (ECG) is an essential, non-invasive diagnostic tool in evaluating cardiac health—especially in diabetic patients, who are at significantly higher risk for both ischemic heart disease and diabetic cardiomyopathy. The value of ECG lies in its ability to detect early electrical or structural changes in the heart, many of which may be asymptomatic due to autonomic neuropathy, a common complication in diabetes that can blunt typical anginal symptoms.

Diabetic patients frequently show a wide range of ECG abnormalities, including:

- **ST-segment and T-wave changes** – which may indicate myocardial ischemia, even in the absence of chest pain
- **Prolonged QT interval** – associated with increased risk of life-threatening arrhythmias and sudden cardiac death
- **Left ventricular hypertrophy (LVH)** – often due to long-standing hypertension and increased cardiac workload

- **Bundle branch blocks or conduction delays** – reflecting altered electrical pathways due to myocardial fibrosis or ischemia
- **Atrial fibrillation** – more prevalent in diabetics, associated with higher risk of stroke and heart failure

The risk of "silent myocardial infarction" is up to four times higher in diabetic individuals. ECG abnormalities may be the first and only indication of prior ischemic events, especially in patients who report no chest pain or typical cardiac symptoms. Routine ECG screening is therefore recommended for diabetic patients, particularly those with longstanding disease, poor glycemic control, or additional cardiovascular risk factors (e.g., hypertension, dyslipidemia, smoking).

Additionally, serial ECGs can help monitor disease progression and treatment efficacy, especially in patients started on medications that affect cardiac conduction (e.g., certain antidiabetic agents or antihypertensives). An abnormal ECG should prompt further investigation through echocardiography, stress testing, or coronary angiography, depending on the findings.

In conclusion, ECG serves as a vital first-line tool in the cardiac assessment of diabetic patients, offering early detection of electrical, structural, and ischemic changes that might otherwise go unnoticed—helping clinicians initiate timely and potentially life-saving interventions.

9. HbA1c (Glycated Haemoglobin) – A Strong Predictor of Retinal Microvascular Damage

HbA1c is a pivotal biomarker for long-term glycemic control and is strongly linked to the onset and progression of diabetic retinopathy (DR), one of the most common and vision-threatening complications of diabetes. Prolonged hyperglycemia leads to biochemical and structural changes in the retinal microvasculature, including capillary basement membrane thickening, pericyte loss, and microaneurysm formation. These pathological changes are directly proportional to the level and duration of elevated HbA1c.

The landmark Diabetes Control and Complications Trial (DCCT) and UKPDS clearly demonstrated that intensive glucose control resulting in lower HbA1c significantly reduces the risk and progression of diabetic retinopathy. An HbA1c level above 7% is consistently associated with increased incidence and severity of retinal lesions, including non-proliferative DR (NPDR) and proliferative DR (PDR).

Mechanistically, elevated glucose enhances the formation of advanced glycation end-products (AGEs), which damage retinal blood vessels by promoting oxidative stress and inflammation. AGEs also impair normal cell signaling in the retina, contributing to vascular leakage, ischemia, and neovascularization—hallmarks of advanced DR.

In clinical practice, HbA1c serves not only as a systemic glycemic control marker but also as a predictor of ocular outcomes. Patients with poorly controlled diabetes and high HbA1c levels should undergo regular retinal screening (typically with fundus photography or dilated eye exams), as they are at significantly higher risk for vision-threatening complications such as macular edema and retinal hemorrhages.

In conclusion, HbA1c remains a cornerstone biomarker in managing and predicting diabetic retinopathy. Maintaining levels below 7% is a critical strategy in preventing vision loss and preserving retinal function in diabetic individuals.

10. Fasting Plasma Glucose (FPG) – Baseline Indicator of Hyperglycemia and Retinal Risk

Fasting Plasma Glucose (FPG) is one of the fundamental tests used in the diagnosis and monitoring of diabetes mellitus. It measures the concentration of glucose in the blood after an overnight fast of at least 8 hours. Persistent elevations in FPG levels are not only diagnostic of diabetes (≥126 mg/dL) but also play a critical role in the development and progression of diabetic retinopathy (DR).

While HbA1c reflects long-term glycemic exposure, FPG provides a snapshot of daily glucose fluctuations, which can also damage retinal capillaries over time. Elevated FPG contributes to endothelial dysfunction, increased vascular permeability, and capillary non-perfusion—all of which are early pathogenic events in the cascade leading to DR. Chronic fasting hyperglycemia promotes oxidative stress and inflammation in retinal tissues, making the microvasculature increasingly fragile and susceptible to hemorrhages, microaneurysms, and ischemia.

Several epidemiological studies have confirmed that patients with consistently high FPG levels are more likely to develop non-proliferative and proliferative diabetic retinopathy, particularly when combined with other risk factors such as hypertension and dyslipidemia. Even in prediabetic individuals (FPG 100–125 mg/dL), there is emerging evidence that subtle retinal changes may begin to occur, especially in genetically predisposed or elderly populations.

Clinically, FPG is used alongside HbA1c to monitor glycemic control. In patients with diabetic retinopathy, poor FPG control is often associated with worsening retinal edema, increased risk of macular ischemia, and a higher likelihood of requiring ophthalmologic interventions such as laser photocoagulation or intravitreal injections.

In summary, FPG, while a basic glycemic parameter, provides essential insights into day-to-day glucose stress on retinal vasculature. Maintaining FPG levels within a normal range (<100 mg/dL) is crucial in reducing retinal complications and preserving vision in individuals with diabetes.

11. Serum VEGF (Vascular Endothelial Growth Factor) – The Molecular Driver of Retinal Neovascularization

Vascular Endothelial Growth Factor (VEGF) is a potent angiogenic cytokine that plays a central role in the pathogenesis of proliferative diabetic retinopathy (PDR) and diabetic macular edema (DME). Under normal conditions, VEGF helps maintain vascular health and supports tissue repair. However, in diabetes, chronic hyperglycemia and retinal ischemia upregulate VEGF expression, especially in hypoxic retinal areas, leading to pathological angiogenesis and increased vascular permeability.

Elevated serum and intraocular VEGF levels have been strongly correlated with the severity of diabetic retinopathy, particularly in the proliferative stage. In PDR, VEGF stimulates the growth of fragile, abnormal new blood vessels on the retina and optic disc, which are prone to rupture and result in vitreous hemorrhages, tractional retinal detachment, and potentially irreversible vision loss. VEGF also increases the permeability of retinal capillaries, contributing to macular edema, the most common cause of vision impairment in diabetic individuals.

Mechanistically, VEGF acts by binding to its receptors (VEGFR-1 and VEGFR-2) on endothelial cells, triggering a cascade that promotes endothelial proliferation, migration, and capillary tube formation. It also disrupts tight junctions between retinal endothelial cells, leading to breakdown of the blood-retinal barrier, a critical event in the early stages of diabetic eye disease.

Clinically, VEGF has become both a biomarker and a therapeutic target. Anti-VEGF therapies (e.g., ranibizumab, bevacizumab, aflibercept) are now standard treatments for PDR and DME, administered via intravitreal injections to reduce neovascularization and retinal swelling. Elevated serum VEGF levels may also serve as an early biomarker for identifying patients at high risk for vision-threatening retinopathy.

In conclusion, VEGF is not merely a bystander but a key molecular driver of disease progression in diabetic retinopathy. Monitoring its levels and targeting its activity have revolutionized the treatment landscape, offering hope for preserving vision in diabetic patients.

12. Retinal Thickness (OCT Scan) – Structural Indicator of Diabetic Macular Edema and Retinal Health

Retinal thickness, typically assessed using Optical Coherence Tomography (OCT), is a crucial non-invasive imaging marker in evaluating and managing diabetic retinopathy (DR), particularly diabetic macular edema (DME). Though not a blood-based biomarker, OCT provides high-resolution, cross-sectional images of the retina, enabling precise measurement of retinal layers and detection of pathological changes caused by chronic hyperglycemia.

In diabetes, prolonged vascular damage due to hyperglycemia leads to breakdown of the blood-retinal barrier, resulting in fluid leakage and accumulation in the macula—the central area of the retina responsible for sharp vision. This causes retinal thickening, which is the hallmark of DME and a leading cause of vision loss in diabetic individuals. OCT quantifies this thickening and can detect even subtle changes long before they are visible via ophthalmoscopy or fundus photography.

The severity of retinal thickening correlates with visual acuity deterioration, and serial OCT scans are used to monitor disease progression or response to treatment. For instance, anti-VEGF therapy or corticosteroid injections are often administered based on OCT findings, with treatment continued or modified depending on whether retinal thickness is reduced.

OCT can also detect subretinal fluid, intraretinal cysts, epiretinal membranes, and tractional changes, all of which contribute to vision impairment and require timely management. Furthermore, emerging OCT technologies, like OCT angiography, now allow visualization of retinal and choroidal vasculature without dye, enhancing our ability to detect capillary non-perfusion, microaneurysms, and neovascularization.

In summary, while not a biochemical marker, retinal thickness via OCT is an

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indispensable structural biomarker for diabetic eye disease. It provides clinicians with real-time, quantitative data that guides diagnosis, prognosis, and treatment decisions—making it a cornerstone in the fight against diabetic vision loss.

13. Albumin-to-Creatinine Ratio (ACR) – A Systemic Marker Reflecting Retinal Microvascular Health

The Albumin-to-Creatinine Ratio (ACR), measured from a spot urine sample, is primarily used as an early marker of diabetic nephropathy, but its significance extends beyond the kidneys. ACR reflects the presence of microalbuminuria, which indicates systemic microvascular damage. Since the retina and kidneys share similar small vessel structures, elevated ACR has been strongly correlated with the development and severity of diabetic retinopathy (DR)—particularly proliferative DR and diabetic macular edema.

In diabetes, chronic hyperglycemia damages the endothelium and basement membranes of small vessels, increasing vascular permeability. This leads to leakage of albumin in the urine (microalbuminuria) and similar leakage of fluids and proteins from retinal capillaries, contributing to retinal thickening, hemorrhages, and exudates. Studies have shown that patients with elevated ACR (>30 mg/g) are at significantly higher risk of developing vision-threatening DR—even before classical ocular symptoms appear.

Elevated ACR is also associated with increased serum VEGF levels and higher levels of systemic inflammation, which further contribute to retinal vascular damage. Clinically, ACR is a low-cost, easily accessible, and highly predictive marker for identifying individuals at risk for microvascular complications, including both nephropathy and retinopathy.

Moreover, tracking ACR over time helps in assessing the effectiveness of interventions aimed at vascular protection, such as RAAS inhibitors (ACE inhibitors/ARBs), which not only lower albuminuria but have been shown to reduce the progression of DR. Patients with concurrent ACR elevation and DR are also at greater risk for cardiovascular events, reinforcing the interconnected nature of diabetic complications.

In conclusion, ACR serves as a powerful systemic biomarker of microvascular injury, linking renal and retinal health. It enables early identification of high-risk patients, allowing for timely ophthalmologic evaluation and integrated care to prevent both kidney failure and irreversible vision loss.

14. Urinary Albumin (Microalbuminuria) – The Earliest Clinical Sign of Diabetic Kidney Injury

Microalbuminuria, defined as the excretion of 30–300 mg of albumin per day in the urine, is often the first detectable marker of diabetic nephropathy, appearing well before any noticeable decline in kidney function. In diabetes, chronic hyperglycemia damages the glomerular basement membrane and impairs the filtration barrier of the kidneys, allowing small amounts of albumin—normally retained in the bloodstream—to leak into the urine.

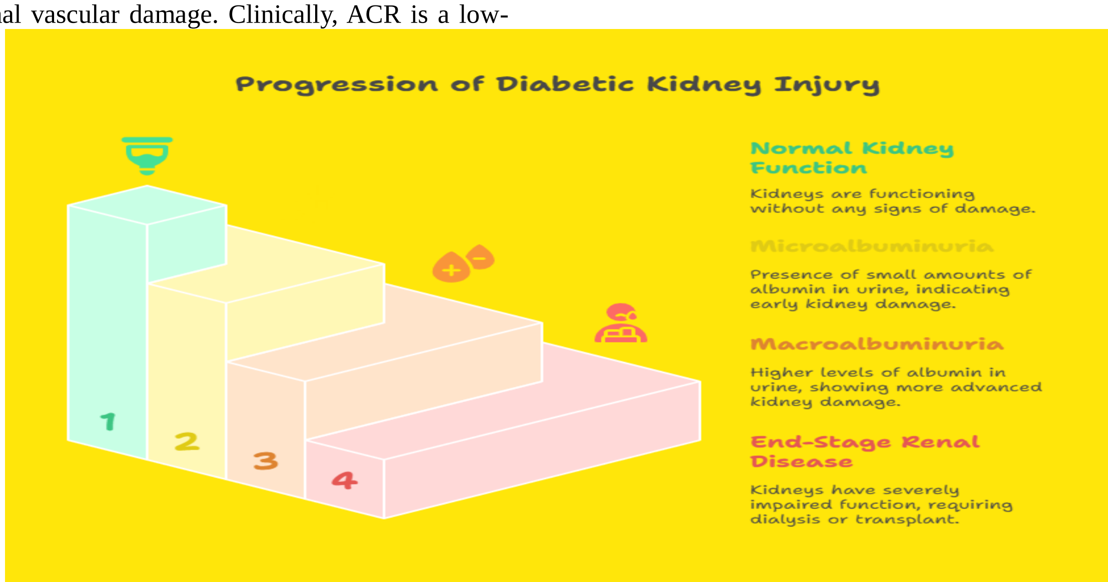

Fig.3. Urinary Albumin (Microalbuminuria) – The Earliest Clinical Sign of Diabetic Kidney Injury

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This early leakage reflects subtle but significant microvascular injury within the glomeruli, the tiny blood-filtering units of the kidney. Without intervention, microalbuminuria can progress to macroalbuminuria (>300 mg/day), eventually leading to nephrotic syndrome, reduced glomerular filtration rate (GFR), and end-stage renal disease (ESRD).

Microalbuminuria is also a systemic marker of endothelial dysfunction, meaning it not only predicts renal complications but also indicates increased cardiovascular risk, including myocardial infarction and stroke. This is particularly concerning in diabetic individuals, where heart and kidney disease frequently coexist and reinforce each other (cardiorenal syndrome).

Clinically, urinary albumin is measured either through 24-hour urine collection, spot urine testing, or more commonly via the albumin-to-creatinine ratio (ACR) for convenience and accuracy. Importantly, the presence of microalbuminuria is often reversible in its early stages through intensive glycemic control, blood pressure regulation (especially with ACE inhibitors or ARBs), and lifestyle interventions.

In conclusion, urinary albumin is a sensitive, early-warning biomarker of diabetic kidney disease. Detecting and treating microalbuminuria promptly is crucial for preventing irreversible nephron loss and preserving long-term renal function in diabetic patients.

15. Albumin-to-Creatinine Ratio (ACR) – The Gold Standard for Early Kidney Damage Screening

The Albumin-to-Creatinine Ratio (ACR) is the preferred, non-invasive test for detecting early kidney damage in individuals with diabetes. It measures the amount of albumin (in mg) relative to creatinine (in g) in a spot urine sample, correcting for variations in urine concentration. An ACR value of 30–300 mg/g is considered microalbuminuria, while values >300 mg/g indicate macroalbuminuria, both of which signal ongoing damage to the glomerular filtration barrier.

Diabetes-induced hyperglycemia causes thickening of the glomerular basement membrane, mesangial expansion, and podocyte injury, which compromise the kidney's ability to retain albumin. As this barrier breaks down, albumin leaks into the urine. ACR is more sensitive and specific than simple dipstick tests and can detect changes before serum creatinine or GFR become abnormal, making it a critical tool for early intervention.

Elevated ACR not only marks the onset of diabetic nephropathy but is also a strong predictor of cardiovascular morbidity and mortality, owing to its association with systemic endothelial dysfunction and inflammation. A progressive rise in ACR reflects worsening kidney damage and often precedes a decline in glomerular filtration rate (GFR).

ACR should be assessed annually in all diabetic patients, starting at diagnosis for type 2 diabetes and five years after diagnosis for type 1 diabetes. Persistent elevation (in at least two out of three tests over three to six months) confirms the presence of diabetic kidney disease.

Therapeutically, interventions such as RAAS inhibition (ACE inhibitors or ARBs), strict glycemic and blood pressure control, and lifestyle changes have been proven to lower ACR and slow the progression of nephropathy.

In summary, ACR is a highly sensitive, reliable, and convenient screening biomarker for diabetic kidney disease, allowing for early detection, risk stratification, and targeted intervention to protect renal and cardiovascular health.

16. Serum Creatinine – Core Marker for Monitoring Renal Function in Diabetes

Serum creatinine is one of the most commonly used biomarkers for evaluating kidney function, particularly in the context of chronic kidney disease (CKD) caused by diabetes. Creatinine is a waste product generated by muscle metabolism and is normally filtered out of the blood by healthy kidneys. When kidney function declines—such as in diabetic nephropathy—serum creatinine levels begin to rise, indicating reduced filtration capacity.

However, serum creatinine alone is not a highly sensitive early marker, since levels can remain within normal limits even after significant nephron loss. This is due to its dependency on several non-renal factors like age, sex, muscle mass, and hydration status. Despite this limitation, it remains essential for calculating estimated glomerular filtration rate (eGFR), which provides a more accurate assessment of renal function.

In diabetic patients, rising serum creatinine often occurs after persistent albuminuria and microvascular damage, signaling progression from early to more advanced stages of kidney disease. At this point, interventions become more about slowing further decline rather than reversing damage. Serum creatinine levels also guide dosing for nephrotoxic drugs or glucose-lowering medications, some of which require renal adjustment (e.g., metformin, SGLT2 inhibitors).

Elevated creatinine levels may also point to acute kidney injury (AKI) superimposed on chronic disease, often triggered by dehydration, infections, or use of NSAIDs—risks that are elevated in poorly controlled diabetic individuals.

In clinical practice, serial monitoring of serum creatinine is used to track disease progression, stage CKD, and guide referral to nephrology. When combined with ACR and eGFR, it provides a comprehensive picture of renal health.

In summary, while not an early marker, serum creatinine is an essential and accessible biomarker for assessing the degree and progression of kidney impairment in diabetes, especially when interpreted in context with other renal indicators.

17. Estimated Glomerular Filtration Rate (eGFR) – Key Indicator of Kidney Filtration Efficiency in Diabetes

Estimated Glomerular Filtration Rate (eGFR) is a crucial measure of how well the kidneys are filtering waste products from the blood. It is calculated using serum creatinine levels along with factors like age, sex, race, and body size, providing a standardized estimate of kidney function. In diabetes, eGFR is vital for staging chronic kidney disease (CKD) and tracking its progression over time.

A normal eGFR is typically ≥90 mL/min/1.73 m², with values between 60–89 indicating mild dysfunction. An eGFR below 60 for more than three months signifies chronic kidney disease, while levels under 30 suggest severe impairment, often necessitating nephrology referral and preparation for renal replacement therapy.

In diabetic nephropathy, a decline in eGFR reflects progressive glomerular damage, often following a period of persistent microalbuminuria. Hyperglycemia-induced injury leads to glomerular hyperfiltration in the early stages, which may initially cause elevated eGFR values—this paradoxical rise is a warning sign of early renal stress. Over time, ongoing damage results in glomerulosclerosis, nephron loss, and irreversible decline in filtration capacity.

eGFR is preferred over serum creatinine alone because it accounts for individual variability and detects significant renal dysfunction before symptoms appear. It also helps adjust drug dosages (especially for nephrotoxic or renally-excreted medications) and assess suitability for certain diabetes treatments like metformin or SGLT2 inhibitors.

Regular monitoring of eGFR in diabetic patients allows for timely intervention with RAAS inhibitors, glycemic and blood pressure control, and lifestyle modifications to slow disease progression and prevent end-stage renal disease (ESRD).

In conclusion, eGFR is a central biomarker in diabetic kidney care, enabling early detection, personalized treatment planning, and improved long-term renal outcomes.

18. BUN (Blood Urea Nitrogen) – Traditional Marker of Kidney Function and Nitrogen Waste in Diabetes

Blood Urea Nitrogen (BUN) is a commonly measured laboratory marker that reflects the amount of nitrogen in the blood derived from urea, a waste product formed during the breakdown of proteins in the liver and excreted by the kidneys. In individuals with diabetes, BUN is routinely used alongside serum creatinine and eGFR to assess renal function and nitrogen waste clearance.

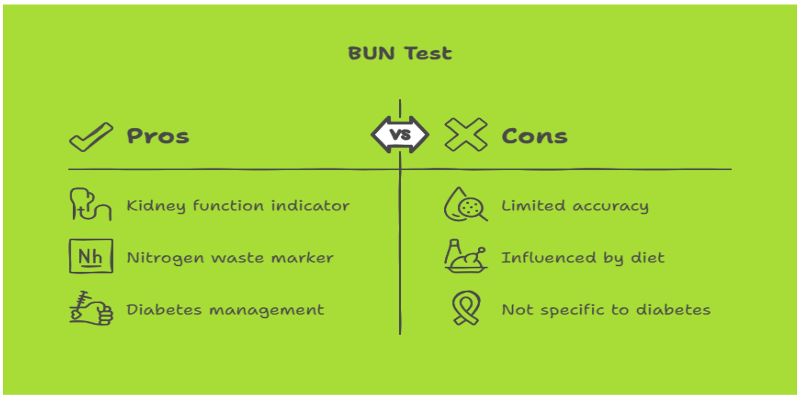

Fig.4. BUN (Blood Urea Nitrogen) – Traditional Marker of Kidney Function and Nitrogen Waste in Diabetes

As diabetic nephropathy progresses and glomerular filtration declines, the kidneys become less effective at eliminating urea from the blood. This leads to elevated BUN levels, which generally correlate with the severity of renal impairment. However, BUN is less specific than creatinine or eGFR, as it can be influenced by several non-renal factors such as dietary protein intake, dehydration, catabolic states, gastrointestinal bleeding, and corticosteroid use.

In early diabetic kidney disease, BUN levels may still remain within normal limits even as albuminuria or mild eGFR decline begins. However, a rising BUN, particularly when accompanied by elevated creatinine and reduced eGFR, strongly indicates advancing renal dysfunction, often corresponding to CKD stages 3–5. The BUN-to-creatinine ratio is also used to help differentiate between prerenal (e.g., dehydration) and intrinsic (e.g., glomerular damage) causes of kidney dysfunction.

Elevated BUN levels are also associated with uremic symptoms such as fatigue, nausea, mental confusion, and poor appetite when kidney function is severely compromised. At this stage, patients may require dialysis planning or renal replacement therapy.

In summary, while not a standalone diagnostic marker, BUN is a valuable supportive indicator of nitrogenous waste buildup and renal clearance efficiency. In diabetes, it complements creatinine and eGFR to offer a broader view of kidney function, hydration status, and disease progression.

19. Cystatin C – A Sensitive and Reliable Alternative to Creatinine for GFR Assessment in Diabetes

Cystatin C is a low molecular weight, non-glycosylated protein produced at a constant rate by all nucleated cells. It is freely filtered by the glomeruli and almost completely reabsorbed and broken down in the renal tubules, without being secreted. Because of these properties, serum cystatin C has emerged as a sensitive and reliable biomarker for estimating glomerular filtration rate (GFR)—especially in diabetic patients where early detection of kidney dysfunction is critical.

Unlike creatinine, cystatin C levels are not significantly affected by muscle mass, age, sex, race, or dietary protein intake, making it particularly valuable in patients with low or abnormal muscle mass (e.g., elderly, malnourished, or cachectic individuals). In diabetic nephropathy, cystatin C may detect mild declines in kidney function even before serum creatinine rises or eGFR drops below normal ranges.

Studies have shown that cystatin C-based eGFR (eGFRcys) is more accurate than creatinine-based estimates in predicting cardiovascular outcomes, progression to end-stage renal disease (ESRD), and all-cause mortality in individuals with diabetes. Moreover, combining creatinine and cystatin C in eGFR calculation (e.g., CKD-EPI combined equation) further improves precision in staging chronic kidney disease.

Cystatin C also reflects systemic inflammation and endothelial dysfunction, both of which are highly relevant in diabetes-related vascular damage. Elevated levels have been associated with higher risks of retinopathy, neuropathy, and cardiovascular disease, making it a potential multisystem biomarker in diabetes management.

Although not yet as widely available or used in routine practice as creatinine, cystatin C testing is increasingly being recommended for patients with borderline kidney function, unexplained changes in creatinine, or discordant eGFR values.

In conclusion, cystatin C is a powerful, early, and stable marker of kidney function in diabetes. It enhances the accuracy of GFR assessment, especially when creatinine is unreliable, and holds promise for more refined detection and monitoring of diabetic kidney disease.

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