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RESEARCH ARTICLE

ASSOCIATION OF VITAMIN D RECEPTOR AND ACE2 RECEPTORS IN TYPE 2 DIABETES MELLITUS CORRELATED WITH CARDIOVASCULAR DISEASE

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Abstract

Type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) are leading contributors to global morbidity and mortality, often coexisting and exacerbating each other's pathophysiology. Recent research highlights the critical roles of the vitamin D receptor (VDR) and the angiotensin-converting enzyme 2 (ACE2) in modulating key processes such as insulin signalling, inflammation, oxidative stress, and endothelial function. Both receptors appear to be pivotal in the shared molecular pathways underlying T2DM and CVD. This review aims to explore the interconnected functions of VDR and ACE2, focusing on their expression across metabolic tissues, regulatory mechanisms, and impact on disease progression. It examines how vitamin D–VDR signalling intersects with the ACE2–Ang-(1–7)– Mas receptor axis, and how this interplay influences glucose homeostasis, vascular integrity, and plaque stability. Key themes include the anti-inflammatory, anti-fibrotic, and endothelial-protective roles of these receptors, as well as the potential of genomic polymorphisms in predicting disease risk and treatment outcomes. Clinical data on biomarkers, imaging correlations, and therapeutic interventions are discussed.

Introduction:-

GLOBAL BURDEN OF T2DM AND CVD:-

Type 2 Diabetes Mellitus (T2DM) and cardiovascular disease (CVD) are among the most pressing global health issues due to their rapidly increasing prevalence and strong clinical interconnection. According to the International Diabetes Federation (2021), an estimated 537 million adults were living with diabetes in 2021, with numbers projected to rise to 783 million by 2045. The majority of these cases are T2DM, which is driven by poor diet, physical inactivity, and rising obesity rates, especially in urbanized regions (Zheng, Ley and Hu, 2018). More than 75% of deaths in people with diabetes result from cardiovascular complications (Rawshani et al., 2017).CVD remains the leading cause of death globally, accounting for approximately 17.9 million deaths each year (World Health Organization, 2021). Individuals with T2DM are at a two- to fourfold higher risk of developing CVD, including myocardial infarction, stroke, and heart failure (Low Wang et al., 2016). A systematic review by Einarson et al. (2018) found that about 32% of individuals with T2DM already present with established CVD at diagnosis.

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Additionally, comorbidity leads to greater healthcare costs and reduced quality of life (Cefalu et al., 2018), underscoring the need for integrated prevention and management strategies.

Pathophysiological Links Between T2DM and CVD:-

Type 2 Diabetes Mellitus (T2DM) and cardiovascular disease (CVD) are closely interconnected through shared and overlapping pathophysiological pathways. Chronic hyperglycemia in T2DM induces endothelial dysfunction and oxidative stress, both of which are major contributors to atherosclerotic plaque development (Brownlee, 2005). Insulin resistance, a defining feature of T2DM, worsens lipid metabolism, resulting in elevated triglycerides, low HDL cholesterol, and small dense LDL particles that are more atherogenic (Goldberg, 2001).

The accumulation of advanced glycation end-products (AGEs), formed as a result of prolonged hyperglycemia, alters protein function and vascular elasticity, thereby promoting inflammation and vascular stiffness (Singh et al., 2001). Additionally, oxidative stress caused by hyperglycemia further reduces nitric oxide bioavailability, impairing vasodilation and promoting hypertension (Ceriello, 2005).

T2DM also enhances platelet reactivity and coagulation, increasing the risk of thrombotic events such as myocardial infarction and stroke (Beckman, Creager and Libby, 2002). Moreover, overactivation of the renin-angiotensin-aldosterone system (RAAS) in diabetic patients contributes to cardiac hypertrophy, fibrosis, and heart failure (Schmieder, 2010).

These interlinked mechanisms demonstrate how T2DM significantly accelerates CVD risk. Therefore, comprehensive management of diabetes must address not only glucose levels but also cardiovascular risk factors to reduce long-term complications.

Importance of Receptor-Mediated Pathways:

Receptor-mediated pathways are central to the pathogenesis of Type 2 Diabetes Mellitus (T2DM) and its cardiovascular complications. The Vitamin D Receptor (VDR) regulates insulin secretion, glucose metabolism, and immune modulation. Studies have shown that impaired VDR signaling is linked to poor glycemic control and increased cardiovascular risk in diabetic patients (Palomer et al., 2008; Bikle, 2014). Vitamin D deficiency, commonly observed in T2DM, further reduces VDR activation, promoting endothelial dysfunction and chronic inflammation (Santoro et al., 2021).

Similarly, the Angiotensin-Converting Enzyme 2 (ACE2) receptor plays a protective role in the cardiovascular system by modulating the renin-angiotensin system (RAS) and reducing oxidative stress (Patel et al., 2016). In diabetic individuals, ACE2 expression is often dysregulated, contributing to vascular injury and cardiac remodeling(Batlle, Jose and Wysocki, 2010). Moreover, ACE2 serves as the entry receptor for SARS-CoV-2, posing added risk for diabetic patients during COVID-19 (Zhou et al., 2020).

Together, these receptors represent critical molecular targets. Modulating VDR and ACE2 activity could provide integrated therapeutic benefits for both metabolic regulation and cardiovascular protection (Santoro et al., 2021; Patel et al., 2016).

Rationale for Focusing on VDR and ACE2:-

The focus on Vitamin D Receptor (VDR) and Angiotensin-Converting Enzyme 2 (ACE2) is rooted in their pivotal roles in bridging metabolic and cardiovascular dysfunctions, particularly in the context of Type 2 Diabetes Mellitus (T2DM) and cardiovascular disease (CVD). VDR, a nuclear hormone receptor, is expressed in pancreatic β-cells, immune cells, and endothelial tissue, where it modulates insulin secretion, inflammatory responses, and vascular health (Palomer et al., 2008; Bikle, 2014). Vitamin D deficiency, which is highly prevalent among individuals with T2DM, contributes to impaired VDR activation, leading to increased oxidative stress, chronic inflammation, and endothelial dysfunction—all of which are known contributors to CVD (Santoro et al., 2021).

ACE2, a transmembrane enzyme and a key regulator of the renin-angiotensin system (RAS), is responsible for converting angiotensin II into the vasodilatory angiotensin 1–7 peptide, thereby promoting anti-inflammatory and cardioprotective effects (Patel et al., 2016). In diabetic conditions, ACE2 expression is dysregulated, tipping the RAS balance toward vasoconstriction, fibrosis, and inflammation (Batlle, Jose and Wysocki, 2010). This contributes to accelerated vascular damage and myocardial remodeling, linking hyperglycemia to heart failure and atherosclerosis.

Moreover, the COVID-19 pandemic has highlighted ACE2's role as the cellular receptor for SARS-CoV-2, amplifying disease severity in diabetic patients (Zhou et al., 2020). Thus, investigating VDR and ACE2 together offers a unique, integrative perspective on the molecular mechanisms that link T2DM and CVD and may uncover dual therapeutic targets to improve both glycemic and cardiovascular outcomes.

Overview of T2DM and Cardiovascular Disease Interplay:

Metabolic Dysregulation in T2DM:

Metabolic dysregulation in Type 2 Diabetes Mellitus (T2DM) involves a combination of insulin resistance, β-cell dysfunction, altered lipid metabolism, chronic inflammation, and oxidative stress. As outlined by DeFronzo (2004) and further supported by Kahn (2003), insulin resistance in peripheral tissues such as skeletal muscle and liver reduces glucose uptake and increases hepatic glucose production, leading to chronic hyperglycemia. To compensate, pancreatic β-cells initially increase insulin output, but this compensatory mechanism deteriorates over time due to glucotoxicity and lipotoxicity, leading to β-cell apoptosis (Prentki and Nolan, 2006; Robertson et al., 2004).

Elevated free fatty acids (FFAs) are key contributors to lipotoxicity and insulin resistance. As noted by Unger and Scherer (2010) and Boden and Shulman (2002), FFAs disrupt insulin signaling pathways, impair mitochondrial oxidation, and increase intracellular lipid accumulation, which negatively affects insulin action. Additionally, Hotamisligil (2006) demonstrated that adipose tissue dysfunction in obesity causes excessive secretion of proinflammatory cytokines such as TNF-α and IL-6, which impair insulin receptor signaling and sustain systemic inflammation.

Dyslipidemia is a prominent feature in T2DM. According to Taskinen (2003) and Goldberg
(2001), insulin resistance alters lipoprotein metabolism, leading to elevated triglycerides, reduced HDL cholesterol, and the formation of small, dense LDL particles, which are more prone to oxidation and atherogenesis. This dyslipidemic profile significantly increases the risk of cardiovascular disease in diabetic individuals (Ginsberg, 2000).

Chronic hyperglycemia leads to the formation of advanced glycation end-products (AGEs), which accumulate in tissues and promote vascular damage. Singh et al. (2001) and Forbes and Cooper (2013) reported that AGEs interact with RAGE (receptor for AGEs), activating inflammatory pathways and contributing to endothelial dysfunction. Brownlee (2005) further proposed oxidative stress as a unifying mechanism of diabetic complications, highlighting the role of ROS generated by mitochondrial dysfunction in tissue injury.

Mitochondrial abnormalities play a crucial role, as described by Lowell and Shulman (2005), where defective oxidative phosphorylation leads to insufficient ATP production and excessive ROS, impairing insulin signaling and promoting cell damage.

Therefore, metabolic dysregulation in T2DM is driven by intertwined processes involving insulin resistance, β-cell failure, lipid toxicity, inflammation, and oxidative stress—each of which contributes significantly to diabetes progression and its cardiovascular consequences.

Mechanisms of Accelerated Atherosclerosis in T2DM:-

Improved atherosclerosis is a trademark of cardiovascular complications in individuals with type 2 Diabetes Mellitus (T2DM), due to a convergence of metabolic, inflammatory, and endothelial abnormalities. chronic hyperglycemia plays a central function by using selling oxidative strain, endothelial dysfunction, and the formation of superior glycation end-products (a while), all of which damage the vascular wall (Brownlee, 2005; Forbes and Cooper, 2013) a while binds to their receptor RAGE on endothelial cells and macrophages, activating NF-κBsignaling and growing expression of adhesion molecules and seasoned-inflammatory cytokines, for that reason perpetuating vascular irritation (Singh et al., 2001; Yan et al., 2009).

Insulin resistance contributes considerably by using disrupting lipid metabolism and growing circulating degrees of atherogenic lipoproteins. This consists of small dense LDL particles, which might be more at risk of oxidation and retention in the arterial wall, enhancing foam cellular formation (Goldberg, 2001; Taskinen, 2003). Oxidized LDL stimulates macrophages and smooth muscle cells, main to plaque development and instability (Glass and Witztum, 2001). moreover, diabetic dyslipidemia also impairs HDL functionality, lowering ldl cholesterol efflux and antioxidant pastime (Kontush and Chapman, 2006). irritation is an crucial motive force of atherosclerosis in T2DM.

Adipose tissue in insulin-resistant states secretes seasoned-inflammatory cytokines which include IL-6, TNF-α, and MCP-1, promoting monocyte recruitment to the endothelium (Hotamisligil , 2006; Donath and Shoelson, 2011). These monocytes differentiate into macrophages, ingest changed lipids, and rework into foam cells—an key step in plaque formation (Libby, 2002).

chronic low-grade irritation also complements vascular smooth muscle cellular proliferation and extracellular matrix transforming, main to fibrous cap thinning and plaque rupture (Hansson, 2005). Endothelial dysfunction, some other hallmark of diabetic vasculopathy, effects from reduced nitric oxide (NO) bioavailability, accelerated endothelin-1, and ROS technology (Ceriello, 2005; Muniyappa and Sowers, 2013). This impairs vasodilation, promotes leukocyte adhesion, and will increase vascular permeability. Platelet hyperactivity and accelerated coagulation in addition promote thrombus formation on ruptured plaques (Beckman, Creager and Libby, 2002). Additionally, the renin-angiotensin-aldosterone machine (RAAS) is overactivated in T2DM, promoting vascular irritation, fibrosis, and oxidative strain (Schmieder, 2010; Zhou et al., 2012). The interaction of those pathways hurries up the atherosclerotic method, making individuals with T2DM to four times much more likely to develop myocardial infarction or stroke (Low Wang et al., 2016) knowledge these multifaceted mechanisms is critical for growing targeted treatment options that deal with both metabolic and vascular components of diabetic atherosclerosis.

Vitamin D Metabolism & VDR Signaling in T2DM:

Vitamin D: Synthesis, Activation, and Systemic Roles:

Vitamin D is an secosteroid hormone critical for calcium homeostasis, bone fitness, and broader physiological features. Its synthesis starts in the skin, in which 7-dehydrocholesterol is transformed to cholecalciferol (vitamin D_3) upon publicity to ultraviolet B (UVB) radiation (Holick, 2007). This precursor is biologically inactive and undergoes two hydroxylation steps: first in the liver via 25-hydroxylase (CYP2R1), forming 25-hydroxyvitamin D [25(OH)D], after which in the kidney with the aid of 1α-hydroxylase (CYP27B1), generating the energetic form, 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] (Jones, 2008;

Christakos et al., 2016). The energetic form binds to the vitamin D receptor (VDR), an nuclear receptor expressed in various tissues such as intestines, kidneys, immune cells, pancreas, heart, and vascular endothelium (Haussler et al., 2011; Norman, 2008) beyond regulating calcium and phosphate metabolism, vitamin D modulates gene expression, immune function, and insulin sensitivity (Bouillon et al., 2008; Pike and Meyer, 2014) vitamin D exerts anti-inflammatory consequences via suppressing pro-inflammatory cytokines consisting of TNF-α and IL-6, while enhancing anti-inflammatory cytokines like IL-10 (Di Rosa et al., 2011).

It additionally plays a function in cardiovascular fitness via regulating renin-angiotensin system (RAS) activity, inhibiting vascular smooth muscle proliferation, and improving endothelial function (Li et al., 2002; Pilz et al., 2009). In metabolic tissues, VDR activation complements insulin secretion and reduces insulin resistance, suggesting an function in the prevention of type 2 Diabetes Mellitus (T2DM) (Maestro et al., 2000; Chiu et al., 2004). consequently, vitamin D is now diagnosed as an pleiotropic hormone influencing both skeletal and additional-skeletal systems, specifically relevant in endocrine and cardiovascular issues.

Structure, Distribution, and Regulation of the Vitamin D Receptor (VDR):

The vitamin D Receptor (VDR) is an member of the nuclear receptor superfamily that features as an ligand-activated transcription aspect. Structurally, VDR incorporates an DNA-binding area (DBD) with two zinc finger motifs and a ligand-binding area (LBD) that helps heterodimerization with the retinoid X receptor (RXR), permitting it to bind to nutrition D reaction elements (VDREs) in target genes (Haussler et al., 2011; Carlberg and Seuter, 2009). VDR is expressed in an wide variety of tissues beyond the classical objectives inclusive of bone, gut, and kidney. greater-skeletal expression consists of pancreatic β-cells, vascular smooth muscle cells, cardiomyocytes, immune cells, and endothelial cells, suggesting an broader physiological position for vitamin D signaling (Bouillon et al., 2008; Norman, 2008).

This large distribution underlies VDR's involvement in numerous procedures which include calcium homeostasis, immune regulation, insulin secretion, and cardiovascular characteristic (Christakos et al., 2016). VDR expression is dynamically regulated at both transcriptional and submit-transcriptional levels. Calcitriol [$1,25(OH)_2D_3$], the lively form of vitamin D, upregulates its personal receptor thru a autoregulatory feedback mechanism (Jones, 2008). additionally, epigenetic elements inclusive of promoter methylation and histone acetylation have an impact on VDR gene expression in ailment contexts like diabetes and atherosclerosis (Dong et al., 2005; Sassi et al., 2018).

Polymorphisms in the VDR gene (e.g., FokI, BsmI, ApaI, TaqI) are associated with altered receptor pastime and had been related to increased susceptibility to T2DM and cardiovascular ailment (Uitterlinden et al., 2004; Maestro et al., 2000). accordingly, the structural complexity, large tissue distribution, and tight regulatory control of VDR spotlight its critical position in mediating the systemic consequences of vitamin D and its capacity as an therapeutic target in metabolic and cardiovascular issues.

VDR's Role in β-Cell Function and Insulin Sensitivity:

Vitamin D, through its receptor (VDR), plays a important role in retaining pancreatic β-cellular function and peripheral insulin sensitivity—both of which might be important to the pathophysiology of type 2 Diabetes Mellitus (T2DM). VDR is expressed in pancreatic β-cells, where it regulates genes involved in insulin biosynthesis and secretion (Maestro et al., 2000; Chertow et al., 1983). Activation of VDR enhances insulin gene expression via binding to vitamin D reaction factors (VDREs) at the human insulin promoter (Bland et al., 2004), and promotes β-cellular survival via reducing cytokine-induced apoptosis (Norman et al., 1980; Zeitz et al., 2003).

In peripheral tissues which include skeletal muscle and adipose tissue, VDR modulates insulin sensitivity through regulation of calcium inflow and glucose transporter activity. Chiu et al. (2004) discovered that individuals with low 25(OH)D levels had increased insulin resistance and impaired β-cellular function, unbiased of BMI. vitamin D enhances insulin receptor expression and promotes insulin-stimulated glucose transport in adipocytes and myocytes (sun and Zemel, 2004; Palomer et al., 2008) moreover, VDR activation downregulates seasoned-inflammatory cytokines like TNF-α and IL-6, which might be recognised to impair insulin signaling pathways (Zemel et al., 2000; Di Rosa et al., 2011) nutrition D also reduces oxidative stress, another contributor to insulin resistance, via growing the expression of antioxidant enzymes which include glutathione peroxidase (Tomaschitz et al., 2010).

Polymorphisms within the VDR gene, which include FokI and BsmI, have been related to altered insulin sensitivity and increased hazard of T2DM, as shown in various population research (Uitterlinden et al., 2004; Riachy et al., 2006). In sum, VDR plays a multifaceted role in regulating both β-cellular function and insulin sensitivity through genomic and non-genomic pathways, making it a compelling healing target for diabetes prevention and control.

VDR-Mediated Anti-inflammatory and Anti-fibrotic Pathways:-

The vitamin D Receptor (VDR), upon activation by 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D$], modulates key transcriptional packages that inhibit infection and fibrosis—primary mechanisms in the pathogenesis of T2DM, atherosclerosis, and cardiorenal syndromes. VDR suppresses the NF-κB pathway, which is understood to modify genes encoding IL-6, IL-1β, and TNF-α, therefore downregulating persistent inflammatory responses in endothelial cells and macrophages (Zhang et al., 2012; Jeffery et al., 2009; Liu et al., 2006). additionally,

$1,25(OH)_2D$-VDR signaling inhibits toll-like receptor (TLR2/4) activation, preventing the initiation of innate immune responses that contribute to insulin resistance and vascular injury (Dickie et al., 2010; Mahon et al., 2003). In monocytes and dendritic cells, VDR activation shifts cytokine profiles towards anti-inflammatory phenotypes by increasing IL-10 and TGF-β manufacturing (Di Rosa et al., 2011; Hewison, 2012). It also promotes regulatory T cell development, enhancing immune tolerance and decreasing persistent infection (Jeffery et al., 2009; Boonstra et al., 2001). VDR is equally vital in anti-fibrotic protection mechanisms. It inhibits TGF-β1-brought about fibroblast activation, decreasing the expression of α-SMA, fibronectin, and collagen sorts I/III in tissues together with the coronary heart, kidneys, and pancreas (Artaza et al., 2009; Alvarez-Diaz et al., 2012;

Andress, 2006). In experimental fashions of diabetic nephropathy, VDR agonists together with paricalcitol and calcitriol drastically downregulated RAS interest and fibrogenic gene expression (Zhou et al., 2012; Kim et al., 2013). furthermore, VDR gene polymorphisms (e.g., TaqI, FokI, BsmI) affect VDR interest and are related to elevated susceptibility to diabetic complications marked by infection and fibrosis (Uitterlinden et al., 2004; Wang et al., 2011; Mishra et al., 2016). collectively, these pathways illustrate how VDR functions as a primary regulator of tissue homeostasis, countering both infection and fibrotic remodeling in metabolic diseases.

ACE2 Receptor Biology and Its Role in T2DM:-

Renin–Angiotensin System Overview and ACE2 Function:-

The renin–angiotensin machine (RAS) is a important regulator of blood stress, fluid stability, and systemic vascular resistance, and its dysregulation performs a pivotal position in the improvement of hypertension, cardiovascular ailment (CVD), and diabetic headaches (Paul et al., 2006). The classical RAS pathway involves the enzymatic

conversion of angiotensinogen to angiotensin I via renin, followed via angiotensin-changing enzyme (ACE)-mediated cleavage of angiotensin I into angiotensin II (Ang II), a amazing vasoconstrictor and seasonedinflammatory peptide (Ferrario and Strawn, 2006).

Ang II acts through the angiotensin II type 1 receptor (AT1R) to set off vasoconstriction, aldosterone release, oxidative pressure, infection, and fibrosis—all of which make contributions to insulin resistance, endothelial dysfunction, and cardiac transforming (Zhou et al., 2012; Oudit and Penninger, 2009). these pathological consequences are substantially amplified in situations consisting of kind 2 diabetes mellitus (T2DM) and metabolic syndrome (de Kloet et al., 2010). In evaluation, angiotensin-changing enzyme 2 (ACE2) represents a counter-regulatory axis in the RAS. ACE2 degrades Ang II into angiotensin-(1–7) [Ang-(1–7)], which exerts vasodilatory, anti-inflammatory, and anti-fibrotic consequences via the Mas receptor (Santos et al., 2003; Patel et al., 2016). This ACE2/Ang(1–7)/Mas axis protects towards Ang II-induced damage via mitigating reactive oxygen species (ROS) formation and inhibiting TGF-β signaling pathways (Gurley et al., 2006; Yisireyili et al., 2017).

ACE2 is abundantly expressed in tissues concerned in metabolic regulation, together with the pancreas, adipose tissue, heart, kidneys, and vasculature, which underscores its systemic significance (Hamming et al., 2004; Tikellis and Thomas, 2012) lack of ACE2 feature in diabetic and hypertensive models leads to more advantageous infection, cardiac hypertrophy, and impaired glucose metabolism (Wysocki et al., 2010; Shoemaker et al., 2019). Given its antagonism of classical RAS overactivity, ACE2 has emerged as a therapeutic target in diabetic cardiovascular complications, with potential benefits in restoring metabolic and endothelial homeostasis (Batlle et al., 2010; Kuba et al., 2010).

ACE2 Expression in Metabolic Tissues:-

Angiotensin-converting enzyme 2 (ACE2) is extensively expressed throughout various metabolic tissues, indicating its vital position in regulating electricity stability, glucose homeostasis, and infection. within the pancreas, ACE2 is normally localized within the islets of Langerhans, in which it modulates nearby renin–angiotensin system (RAS) activity to guard β-cells from oxidative pressure and infection (Bindom and Lazartigues, 2009; Roca-Ho et al., 2017). Its expression allows keep insulin secretion and pancreatic characteristic below diabetic conditions (Wysocki et al., 2010). In adipose tissue, ACE2 is upregulated in response to excessive-fat diets, appearing to counteract angiotensin II (Ang II)-precipitated infection and insulin resistance (Gupte et al., 2008; Shoemaker et al., 2019) increased ACE2 expression facilitates conversion of Ang II to Ang-(1–7), thereby enhancing adiponectin secretion and improving insulin sensitivity (Santos et al., 2003). within the liver, ACE2 modulates lipid metabolism and steatosis.

Its deficiency has been related to hepatic insulin resistance and increased gluconeogenesis (Xia and Lazartigues, 2010). In skeletal muscle, ACE2 impacts glucose uptake and mitochondrial characteristic, doubtlessly mitigating insulin resistance (Fernandes et al., 2020). The heart and vascular endothelium also show excessive ACE2 expression, in which it acts protectively towards diabetic cardiomyopathy and vascular infection (Hamming et al., 2004; Patel et al., 2016). Given this widespread distribution, ACE2 serves as an important modulator of metabolic homeostasis, making it an key goal in coping with diabetes-related headaches.

ACE2 in Glucose Homeostasis and Insulin Secretion:-

Angiotensin-changing enzyme 2 (ACE2) performs a critical role in regulating glucose homeostasis and insulin secretion, on the whole through its modulation of the renin– angiotensin machine (RAS) and interplay with the Ang-(1–7)/Mas receptor axis. with the aid of degrading angiotensin II (Ang II), ACE2 reduces oxidative pressure and infection in pancreatic islets—elements acknowledged to impair insulin biosynthesis and secretion (Bindom and Lazartigues, 2009; Chhabra et al., 2013). research in diabetic mice have proven that ACE2 deficiency consequences in glucose intolerance, reduced insulin sensitivity, and exacerbated β-cellular dysfunction (Wysocki et al., 2010; Tikellis et al., 2004). within the pancreas, ACE2 is expressed in each β- and α-cells, and its upregulation enhances the local conversion of Ang II to Ang-(1–7), a peptide that improves islet vascularization and insulin exocytosis (Roca-Ho et al., 2017; Santos et al., 2003).

Activation of the Mas receptor with the aid of Ang-(1–7) stimulates insulin signalling pathways, including PI3K/Akt, and promotes glucose uptake in peripheral tissues along with skeletal muscle and adipose tissue (Shao et al., 2008; Fernandes et al., 2020). moreover, ACE2/Mas activation reduces ranges of seasonedinflammatory cytokines like TNF-α and IL-6, which interfere with insulin receptor phosphorylation and downstream signaling (Yisireyili et al.,

2017). In transgenic models, overexpression of ACE2 has been related to advanced glucose tolerance, more suitable firstsegment insulin response, and safety against eating regimen-brought about insulin resistance (Shoemaker et al., 2019; Batlle et al., 2010). for this reason, ACE2 no longer simplest counteracts the deleterious outcomes of Ang II but also at once supports insulin biosynthesis, secretion, and movement, making it a promising therapeutic target in diabetes control**.**

ACE2 and Endothelial Dysfunction in Diabetes:
Endothelial disorder is an key early occasion within the improvement of diabetic vascular complications, driven by hyperglycemia-precipitated oxidative stress, irritation, and impaired nitric oxide (NO) bioavailability (Giacco and Brownlee, 2010). Angiotensin-converting enzyme 2 (ACE2) plays an defensive role by mitigating these methods via its regulation of the renin–angiotensin system (RAS). by degrading angiotensin II (Ang II) into angiotensin-(1–7) [Ang-(1–7)], ACE2 prevents Ang II-mediated endothelial damage, along with vasoconstriction, oxidative stress, and irritation (Patel et al., 2016; Santos et al., 2003).

In diabetes, decreased ACE2 expression and activity in endothelial cells exacerbate vascular disorder, selling leukocyte adhesion, endothelial activation, and thrombosis (Tikellis et al., 2012; Wysocki et al., 2010). restoration of ACE2 hobby in experimental diabetic models improves endothelial nitric oxide synthase (eNOS) feature, reduces VCAM-1 and ICAM-1 expression, and attenuates vascular irritation (Cheng et al., 2012; Zhang et al., 2014). The ACE2/Ang-(1–7)/Mas axis has been shown to counterbalance the pro-inflammatory AT1R signaling by activating Mas receptor-mediated PI3K/Akt-eNOS pathways, improving NO manufacturing and endothelial survival (Gallagher et al., 2008; Jiang et al., 2013). moreover, Ang-(1–7) increases endothelium-structured vasodilation and decreases ROS tiers, preserving vascular tone in diabetic mice (Santos et al., 2008; Yisireyili et al., 2017). scientific research have also reported inverse correlations among circulating ACE2 tiers and markers of endothelial damage in T2DM patients (Lovren et al., 2010). these findings highlight ACE2 as an ability therapeutic target to save you or reverse endothelial disorder in diabetes-related cardiovascular ailment.

Cross-Talk between VDR and ACE2 Signaling Pathways:
Molecular Intersections: NF-κB, MAPK, and RAS Modulation:
The vitamin D receptor (VDR) and angiotensin-converting enzyme 2 (ACE2) intersect key molecular pathways—NF-κB, MAPK, and the renin–angiotensin gadget (RAS)—that power infection, fibrosis, and insulin resistance in T2DM and CVD. The NF-κB pathway, a vital regulator of inflammatory gene expression, is activated in diabetic tissues by using hyperglycemia and oxidative strain, selling IL-6, TNF-α, and MCP-1 manufacturing (Giacco and Brownlee, 2010). VDR activation suppresses NF-κBsignaling by using inhibiting IκBα degradation, thereby decreasing inflammatory cytokine expression (Zhang et al., 2012; Jeffery et al., 2009). further, ACE2 overexpression attenuates NF-κB interest by using degrading Ang II, a key upstream activator of this pathway, into Ang-(1–7), which exerts anti-inflammatory outcomes through the Mas receptor (Tikellis et al., 2012; Gallagher et al., 2008).

The MAPK pathway, which includes ERK, JNK, and p38 kinases, is likewise implicated in insulin resistance and endothelial dysfunction. Hyperactivation of JNK and p38 MAPK in adipose and vascular tissues contributes to insulin receptor substrate (IRS) serine phosphorylation and reduced glucose uptake (Hirosumi et al., 2002). both VDR signaling and ACE2/Ang-(1–7) axis downregulate MAPK phosphorylation, improving insulin sensitivity and decreasing vascular infection (Shao et al., 2008; Chandel et al., 2013). The RAS integrates with both NF-κB and MAPK. Ang II stimulates AT1R to set off oxidative strain, apoptosis, and inflammatory gene expression through both pathways (Ferrario and Strawn, 2006). In comparison, VDR in a roundabout way suppresses RAS by using decreasing renin gene expression, for that reason restricting Ang II formation (Li et al., 2002), even as ACE2 directly shifts the stability closer to the protective Ang-(1–7)/Mas signaling, which inhibits NADPH oxidase, NF-κB, and p38 MAPK interest (Santos et al., 2008; Yisireyili et al., 2017). Collectively, these converging actions of VDR and ACE2 on the molecular level spotlight their synergistic capability in modulating diabetic and cardiovascular pathophysiolog.

Vitamin D's Influence on ACE2 Expression and Activity:-
Latest research has found out that vitamin D not most effective performs an classical role in calcium metabolism but additionally modulates the renin–angiotensin system (RAS) by means of influencing ACE2 expression and enzymatic activity, specifically below pathological conditions which include type 2 diabetes mellitus (T2DM) and cardiovascular ailment (CVD). 1,25-dihydroxyvitamin D_3 (calcitriol), the lively form of vitamin D, exerts its biological outcomes through the vitamin D receptor (VDR), an nuclear transcription thing that regulates gene

expression. substantially, VDR activation has been shown to upregulate ACE2 mRNA and protein expression in more than one tissues inclusive of the lungs, coronary heart, and kidneys (Xu et al., 2017; Dancer et al., 2015).

This upregulation consequences in improved conversion of pro-inflammatory angiotensin II (Ang II) to angiotensin-(1–7), which exerts anti-inflammatory, anti-fibrotic, and vasodilatory effects (Santos et al., 2003; Liu et al., 2020).
In diabetic models, vitamin D supplementation has tested an defensive role by means of restoring ACE2 expression within the pancreas and vasculature, attenuating infection, and improving insulin sensitivity (Chilton et al., 2015; Lin et al., 2012). moreover, vitamin D suppresses renin gene transcription, thereby not directly lowering Ang II formation and moving the RAS balance in the direction of the ACE2/Ang-(1–7)/Mas axis (Li et al., 2002). Human research help these findings. Serum vitamin D levels definitely correlate with ACE2 expression and negatively with inflammatory biomarkers in patients with diabetes and hypertension (Panarese and Shahini, 2020). moreover, calcitriol has been shown to reduce endothelial disorder by means of growing ACE2 and eNOS expression, thereby improving nitric oxide bioavailability and vascular relaxation (Liu et al., 2019). Given these multifaceted effects, vitamin D serves as both an modulator and enhancer of ACE2 expression and function, offering an healing opportunity to restore RAS balance and decrease cardiometabolic chance in T2DM.

ACE2 Regulation of Local Vitamin D Metabolism:
Rising evidence highlights the bidirectional courting among ACE2 and vitamin D metabolism, suggesting that ACE2 now not only responds to vitamin D signalling however additionally influences neighbourhood vitamin D activation in metabolic tissues. This interplay is mainly crucial inside the context of T2DM and CVD, in which both pathways are frequently dysregulated. ACE2 contributes to the preservation of a favourable anti-inflammatory environment, that is crucial for nearby activation of vitamin D.

Inflammatory cytokines inclusive of TNF-α and IL-6 can downregulate CYP27B1, the enzyme that converts 25hydroxyvitamin D to its lively form 1,25-dihydroxyvitamin D_3 (calcitriol) (Zhang et al., 2012). through reducing oxidative strain and irritation via the Ang-(1–7)/Mas receptor axis, ACE2 circuitously promotes the activity of CYP27B1 and inhibits CYP24A1, that is answerable for calcitriol degradation (Li et al., 2004; Santos et al., 2008) studies in ACE2-poor mice have proven decreased expression of vitamin D-activating enzymes in renal and vascular tissues, contributing to reduced calcitriol stages and impaired tissue-precise vitamin D signaling (Xia and Lazartigues, 2010; Wysocki et al., 2010). Conversely, overexpression of ACE2 has been related to extended nearby and systemic calcitriol stages, suggesting a high-quality feedback loop that enhances nutrition D bioactivity (Xu et al., 2017). furthermore, ACE2 appears to beautify VDR expression in target tissues inclusive of the heart and pancreas, which amplifies vitamin D's downstream anti-inflammatory and metabolic results (Chen et al., 2020). This reinforces the healing potential of ACE2 now not only in RAS regulation however additionally in optimizing vitamin D signaling pathways for metabolic and cardiovascular protection.

Summarizing the Bidirectional Feedback Loop:-
The interplay between ACE2 and vitamin D signaling represents an important bidirectional remarks loop within the law of metabolic and cardiovascular homeostasis. On one hand, vitamin D, through VDR activation, enhances ACE2 expression and interest, shifting the renin– angiotensin system (RAS) closer to its shielding arm—Ang-(1–7)/Mas receptor—which exerts anti-inflammatory, anti-fibrotic, and insulin-sensitizing outcomes (Xu et al., 2017; Liu et al., 2020). however, ACE2, by means of lowering oxidative strain and inflammatory cytokine load, promotes neighborhood diet D activation by means of enhancing CYP27B1 and suppressing CYP24A1, thereby maintaining calcitriol bioavailability (Wysocki et al., 2010; Li et al., 2004). This synergistic dating reinforces VDR-mediated gene expression, improves insulin sensitivity, and protects in opposition to endothelial disorder and β-cellular failure in T2DM (Chen et al., 2020; Tikellis et al., 2012). knowledge this loop offers novel insight into dual-targeted therapeutic strategies for metabolic and cardiovascular illnesses.

Impact of VDR and ACE2 Modulation on CVD Risk in T2DM:
Anti-Atherogenic Effects via VDR Activation:
Activation of the vitamin D receptor (VDR) performs an critical defensive position in mitigating atherosclerosis, specifically in individuals with type 2 diabetes mellitus (T2DM) and related cardiovascular ailment (CVD). VDR activation modulates lipid metabolism, inhibits vascular inflammation, and preserves endothelial integrity—hallmarks of an antiatherogenic phenotype (Talmor et al., 2008; Chen et al., 2015). one of the primary mechanisms involves inhibition of pro-inflammatory signaling pathways.

VDR ligation with the aid of 1,25dihydroxyvitamin D_3 suppresses the nuclear issue kappa-mild-chain-enhancer of activated B cells (NF-κB) and MAPK pathways, decreasing expression of VCAM-1, ICAM-1, IL-6, and TNF-α in endothelial and vascular smooth muscle cells (Jeffery et al., 2009; Zhang et al., 2012). these cytokines and adhesion molecules are vital to monocyte recruitment and plaque formation in the atherosclerotic vessel wall (Libby et al., 2011). In macrophages, VDR activation shifts the phenotype from seasoned-atherogenic M1 to anti-inflammatory M2, contributing to plaque stability and regression (Wang et al., 2012). additionally, VDR signaling downregulates foam cell formation with the aid of suppressing scavenger receptor-an (SR-an) and CD36 expression while upregulating cholesterol efflux transporters like ABCA1 and ABCG1 (Oh et al., 2009).

Importantly, VDR additionally helps endothelial nitric oxide synthase (eNOS) expression and nitric oxide (NO) bioavailability, which assist keep vascular tone and save you endothelial dysfunction, an early marker of atherogenesis (Andrukhova et al., 2014; Talmor et al., 2008). nutrition D deficiency, conversely, is associated with improved carotid intima-media thickness, higher coronary artery calcium rankings, and more cardiovascular event charges in epidemiological studies (Wang et al., 2008; Pilz et al., 2010). these findings underscore the anti-atherogenic ability of VDR activation, positioning it as an compelling therapeutic goal for diabetic and cardiovascular complications.

Cardioprotective Roles of the ACE2–Ang-(1–7) Axis:
The ACE2–Angiotensin-(1–7) [Ang-(1–7)]–Mas receptor axis plays an imperative function in cardioprotection, mainly inside the context of type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD). This axis counterbalances the classical ACE–Angiotensin II (Ang II)–AT1 receptor pathway, which promotes vasoconstriction, oxidative pressure, infection, fibrosis, and endothelial dysfunction (Santos et al., 2008; Ferrario and Strawn, 2006). ACE2 cleaves Ang II into Ang-(1–7), an heptapeptide that binds to the Mas receptor, activating signaling pathways that sell vasodilation, anti-inflammatory, anti-apoptotic, and antiproliferative outcomes inside the cardiovascular system (Donoghue et al., 2000; Gallagher et al., 2008). In each experimental and medical models of hypertension, T2DM, and heart failure, upregulation of ACE2 or Ang-(1–7) management has been proven to reduce cardiac hypertrophy, attenuate interstitial fibrosis, and enhance left ventricular characteristic (Gurley et al., 2006; Patel et al., 2016).

Mechanistically, Ang-(1–7) enhances endothelial nitric oxide synthase (eNOS) activation through PI3K/Akt signaling, thereby growing nitric oxide (NO) bioavailability and enhancing endothelial characteristic (Jiang et al., 2013; Yisireyili et al., 2017). simultaneously, Ang-(1–7) inhibits NADPH oxidase–mediated ROS production, suppresses NF-κB activation, and downregulates seasoned-fibrotic mediators including TGFβ1 and collagen I (Zhong et al., 2010; Chappell, 2007). ACE2 expression is likewise upregulated beneath caloric limit, workout, and vitamin D supplementation, all of which can be related to superior cardiovascular outcomes (Ferreira et al., 2009; Xu et al., 2017). Conversely, ACE2 deficiency or dysfunction exacerbates cardiac harm, endothelial impairment, and metabolic dysregulation, mainly in diabetic states (Wysocki et al., 2010; Tikellis et al., 2012). Taken together, the ACE2–Ang-(1–7) axis represents an compensatory, cardioprotective mechanism that mitigates RAS overactivation and gives healing promise in T2DM-related cardiovascular complications.

Synergistic Effects on Endothelial Health and Plaque Stability:
The vitamin D–VDR axis and the ACE2–Angiotensin-(1–7)–Mas receptor axis act synergistically to maintain endothelial integrity and promote plaque balance, vital in preventing atherosclerotic progression in patients with type 2 diabetes mellitus (T2DM) and cardiovascular sickness (CVD). vitamin D, thru VDR activation, complements endothelial nitric oxide synthase (eNOS) expression, thereby increasing nitric oxide (NO) bioavailability and enhancing vascular rest (Andrukhova et al., 2014). simultaneously, ACE2-derived Ang-(1– 7) turns on the Mas receptor, which similarly stimulates PI3K/Akt-eNOSsignaling, reducing oxidative pressure and endothelial apoptosis (Jiang et al., 2013; Santos et al., 2008).
This twin law reinforces endothelial barrier function and reduces monocyte adhesion, hence limiting early atherogenesis (Zhang et al., 2012) within the atherosclerotic plaque, both pathways modulate macrophage activity. VDR signaling shifts macrophage polarization from seasonedinflammatory M1 to anti-inflammatory M2, assisting plaque stabilization (Wang et al., 2012). concurrently, Ang-(1–7) suppresses matrix metalloproteinases (MMPs) and seasonedinflammatory cytokines like TNF-α and IL-6, reducing plaque rupture danger (Zhong et al., 2010). moreover, VDR and ACE2 mutually inhibit the NF-κB and MAPK pathways, downregulating VCAM-1, ICAM-1, and oxidized LDL uptake, which might be key contributors to endothelial disorder and plaque instability (Jeffery et al., 2009; Tikellis et al., 2012). collectively, these intertwined mechanisms demonstrate how VDR and ACE2 act

cooperatively to guard endothelial cells, lessen infection, and stabilize plaques—highlighting their capability as combined therapeutic targets in diabetic vascular sickness.

Clinical Correlations: Serum Biomarkers & Imaging:
Clinical evidence supports strong correlations between vitamin D and ACE2 stages with key cardiovascular biomarkers and imaging parameters. Low serum 25-hydroxyvitamin D [25(OH)D] concentrations are appreciably associated with expanded high-sensitivity Creactive protein (hs-CRP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), reflecting systemic irritation and endothelial disorder in patients with type 2 diabetes mellitus (T2DM) and atherosclerosis (Wang et al., 2008; Pilz et al., 2010). Conversely, enough vitamin D reputation has been linked with progressed go with the flow-mediated dilation (FMD) and reduced carotid intima-media thickness (cIMT), both non-invasive markers of vascular health (Talmor et al., 2008). moreover, higher ACE2 pastime in plasma correlates with better left ventricular ejection fraction (LVEF) and reduced arterial stiffness, as proven in both diabetic and heart failure patients (Ramchand et al., 2020). Imaging strategies including cardiac MRI and coronary artery calcium scoring similarly screen inverse institutions between vitamin D/ACE2 stages and plaque burden, reinforcing their prognostic value in clinical practice (Chen et al., 2015).

Therapeutic Implications & Clinical Interventions:
Vitamin D Supplementation Trials in T2DM/CVD:
Several clinical trials have evaluated the impact of vitamin D supplementation on metabolic and cardiovascular outcomes in type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD), with mixed but promising results.
In the D2d trial, supplementation with 4,000 IU/day of vitamin D_3 in individuals with prediabetes resulted in a 12% reduction in progression to T2DM, although the primary endpoint was not statistically significant (Pittas et al., 2019). However, subgroup analysis revealed greater benefit among those with low baseline vitamin D levels (Pittas et al., 2020).

Vitamin D has also shown modest improvement in glycemic control, with meta-analyses reporting reduced HbA1c, improved insulin sensitivity, and lower fasting glucose levels following supplementation in vitamin D-deficient patients (Mitri et al., 2011; George et al., 2012).

Cardiovascular benefits have been observed in trials where vitamin D improved endothelial function, reduced inflammatory biomarkers, and lowered blood pressure, especially in hypertensive or diabetic cohorts (Talmor et al., 2008; Zittermann et al., 2017). However, largescale studies like VITAL did not show significant reduction in CVD events overall (Manson et al., 2019), indicating that baseline deficiency, dose, and duration are critical factors influencing outcomes.

ACE2-Targeted Agents and RAS Blockers:
Healing modulation of the renin–angiotensin gadget (RAS) has long been critical to handling cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM). conventional RAS blockers, inclusive of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs), exert protecting results by lowering Ang II–mediated vasoconstriction, inflammation, and fibrosis (Yusuf et al., 2000; Brenner et al., 2001). but, their indirect have an effect on on ACE2–Ang-(1–7)–Mas receptor signaling has sparked interest in more ACE2-unique healing techniques. Recombinant human ACE2 (rhACE2) has been shown in preclinical models to reduce oxidative pressure, enhance cardiac feature, and suppress diabetic nephropathy and atherosclerosis by enhancing Ang-(1–7) availability (Batlle et al., 2010; Wysocki et al., 2010). although early-phase human trials confirmed rhACE2 to be secure and biologically energetic (Haschke et al., 2013), large-scale cardiovascular final results research are missing. moreover, ACE2 activators inclusive of XNT and DIZE (diminazene aceturate) have confirmed anti inflammatory and antifibrotic results in animal models of high blood pressure and diabetes (Kulemina and Ostrov, 2011; Soler et al., 2009). ARBs, in particular telmisartan and losartan, may additionally upregulate ACE2 expression, imparting dual RAS modulation blessings (Zhong et al., 2010). these findings highlight ACE2 as a viable healing goal in T2DM-associated cardiovascular complications, warranting similarly medical validation.

Combined/Adjunctive Strategies and Safety:
Given the overlapping and synergistic roles of the vitamin D–VDR and ACE2–Ang-(1–7) pathways, adjunctive treatment plans targeting both axes have emerged as a promising technique for type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) control. Coadministration of vitamin D supplements with RAS blockers, along with ACE inhibitors or ARBs, has proven better efficacy in improving endothelial feature and decreasing irritation,

compared to monotherapy (Krause et al., 2015; Kim et al., 2012). vitamin D may also upregulate ACE2 expression, restoring the balance among Ang II and Ang-(1–7), thereby improving the protecting arm of the RAS system (Xu et al., 2017; Liu et al., 2020).

This aggregate may also make bigger anti inflammatory, anti-fibrotic, and insulin-sensitizing outcomes, which can be vital in stopping diabetic complications. From an protection angle, both vitamin D and RAS blockers are well-tolerated in maximum populations. but, care must be taken to avoid hypercalcemia or hyperkalemia, specifically in patients with renal impairment (Pilz et al., 2010; Wysocki et al., 2010). monitoring of electrolytes, serum 25(OH)D, and renal feature is important when combining those agents in scientific practice. average, twin-centered therapy represents a rational, secure, and doubtlessly superior approach for mitigating T2DMrelated cardiovascular threat.

Research Gaps & Future Directions:

Mechanistic In Vivo and In Vitro Studies Needed:

Regardless of huge observational and clinical insights, in addition mechanistic research are important to clarify the molecular crosstalk among vitamin D–VDR signaling and the ACE2– Ang-(1–7)–Mas receptor axis in the context of type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD). future in vitro research should attention on delineating how VDR activation modulates ACE2 gene expression in particular cellular types consisting of endothelial cells, adipocytes, and pancreatic β-cells (Liu et al., 2020; Xu et al., 2017). further, in vivo animal models of T2DM with VDR or ACE2 knockout or overexpression should resolve tissue-particular outcomes, and perceive key regulatory nodes consisting of NF-κB, PI3K/Akt, and MAPK pathways (Chen et al., 2015; Santos et al., 2008). Those models may additionally clarify the temporal series of molecular activities and assist optimize dose, timing, and synergistic interventions focused on both pathways. Such insights are critical to establish causality and translate findings into powerful therapies.

Genomic Variants of VDR and ACE2 for Personalized Medicine:

knowledge genetic polymorphisms within the VDR and ACE2 genes may offer valuable insights into individual susceptibility to type 2 diabetes mellitus (T2DM) and cardiovascular sickness (CVD), and manual the improvement of personalized cures. variants within the VDR gene, inclusive of FokI, BsmI, TaqI, and ApaI, were associated with altered vitamin D responsiveness, insulin sensitivity, and inflammatory profiles in various populations (Zhang et al., 2012; Karonova et al., 2018). similarly, ACE2 gene polymorphisms, including rs2106809 and rs4646142, are linked to variations in ACE2 expression and Ang-(1–7) activity, influencing blood strain regulation and metabolic consequences(Kara, M., Ekiz, T., Ricci, V., Kara, Ö., Chang, K.V. and Özçakar, L., 2020). 'Scientific Strabismus' or two related pandemics: coronavirus disease and vitamin D deficiency. British Journal of Nutrition, 124(7. these genetic variants may in part explain interindividual variability in response to vitamin D supplementation or RAS-targeted cures. Integrating genomic screening into medical protocols may want to help tailor interventions primarily based on receptor expression profiles, marking a step closer to precision medicinal drug in T2DM and CVD management.

Designing Large-Scale, Longitudinal Clinical Trials:

To translate mechanistic and observational findings into scientific practice, there may be a urgent need for huge-scale, longitudinal trials assessing the blended effect of vitamin D and ACE2-modulating treatments on T2DM and CVD effects. Trials need to stratify participants by means of baseline vitamin D reputation, genetic polymorphisms, and metabolic threat elements, with long-time period follow-up of vascular activities, glycemic manage, and mortality. (Kara, M., Ekiz, T., Ricci, V., Kara, Ö., Chang, K.V. and Özçakar, L., 2020). Integrating multi-omics, imaging, and biomarker profiling will enhance mechanistic understanding and manual precision medicine processes.

Conclusion:-

The dynamic interaction between the vitamin D receptor (VDR) and the ACE2–Angiotensin(1–7)–Mas receptor axis gives essential insights into the pathophysiology linking type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD). these two signaling pathways converge on shared mechanisms which includes infection regulation, oxidative pressure reduction, endothelial safety, and metabolic control, imparting an holistic framework for information disorder development. proof shows that modulating each VDR and ACE2 pathways may also provide twin benefits: enhancing insulin sensitivity and β-cell characteristic whilst simultaneously reducing vascular damage and plaque instability. This positions them not best as therapeutic targets but also as emerging biomarkers for disorder hazard, prognosis, and treatment responsiveness.

The identification of genetic polymorphisms in each receptors similarly helps the potential for personalised medication, allowing stratification of patients primarily based on their genomic profiles and receptor expression patterns. furthermore, integrating vitamin D supplementation with ACE2-enhancing strategies ought to shape the premise for mixed interventions that focus on each metabolic and vascular complications in T2DM. In conclusion, the VDR–ACE2 axis represents a promising avenue for translational research and clinical innovation, with potential to reshape the prevention and management of T2DM-associated cardiovascular diseases in the era of precision medicine.

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