# Wnt Signaling to Vascular Complications in T2DM

Vascular complications are the leading cause of morbidity and mortality among patients with type 2 diabetes mellitus (T2DM). These vascular abnormalities result in a chronic hyperglycemic state, which influences many signaling molecular pathways that initially lead to increased oxidative stress, increased inflammation, and endothelial dysfunction, leading to both microvascular and macrovascular complications. Endothelial dysfunction represents the initial stage in both types of vascular complications; it represents "mandatory damage" in the development of microvascular complications and only "introductory damage" in the development of macrovascular complications. Increasing scientific evidence has revealed an important role of the Wnt pathway in the pathophysiology of the vascular wall. It is well known that the Wnt pathway is altered in patients with T2DM.

1. Wnt Signaling Pathway in the Vasculature

All organs depend on blood vessels for oxygen and nutrients. The vasculature of each organ is structurally and molecularly different. The control of organ-specific vascularization and endothelial cell differentiation is controlled by intracellular signaling pathways. Although the best known vascular signaling pathways are vascular endothelial growth factor/vascular endothelial growth factor receptor (VEGF/VEGFR) and angiopoietin/Tie2, a growing body of literature points to the Wingless-Int (Wnt) signaling pathway as an essential component in vascular development [1]. As emerged from loss- and gain-of-function experimental models, Wnt signaling might contribute to vascular development and homeostasis [2].

The Wnt signaling pathway is made up of proteins that transmit signals from the extracellular to the intracellular matrix. These components are included in three pathway types: canonical pathway, noncanonical cell polarity pathway, and noncanonical calcified pathway [3][4] (**Figure 1**).
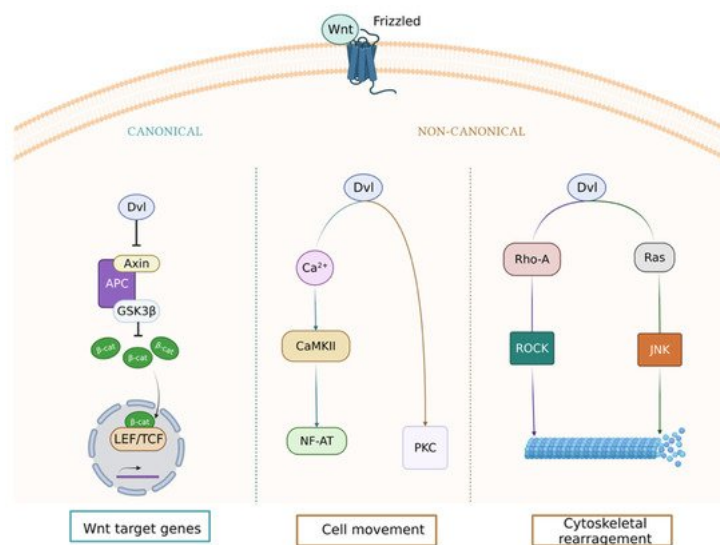
Figure 1. Canonical and noncanonical (Wingless-Int) Wnt signaling pathways. These pathways are activated when a Wnt ligand binds to the Frizzled (Fzd) receptor. The active canonical pathway is mediated by β-catenin, which translocates to the nucleus and acts as a coactivator of the transcription factor T-cell factor/lymphoid enhancer factor family (TCF/LEF), leading to upregulation of Wnt target genes. The two main noncanonical pathways are the Wnt/calcium and planar cell polarity (PCP) pathways. In the Wnt/calcium pathway, Wnt binding to Fzd activates Disheveled (Dvl), which stimulates calcium release from the endoplasmic reticulum, activating protein kinase C (PKC) and calmodulin-dependent kinase II (CamKII) and, in turn, the transcription factor nuclear factor of activated T cells (NFAT). The Wnt/PCP pathway is mediated by the Ras homolog family member A (RhoA) and Ras guanosine triphosphatases (GTPases) that lead to the activation of the RhoA/Rho-associated kinase (ROCK) or N-terminal kinase (JNK) axis. Created with BioRender.com.

The canonical pathway is the best characterized at present, and it is involved in mediating fundamental biological processes such as embryogenesis, organogenesis, and tumorigenesis [1]. Initially, it was fundamentally linked to the regulation of bone formation, but the evidence currently points to an important role at the vascular level.

Skeletal integrity is maintained by a balance between bone resorption and bone formation, a process called bone remodeling [5]. Runx2 is a target gene of Wnt signaling, and activation of Runx2 by Wnt stimulates osteoblast differentiation and bone formation [6][7]. Expression of Runx2 begins in uncommitted stem cells, increases in osteoblast precursors, peaks in immature osteoblast, and decreases once osteoblasts mature [8]. This expression of Runx2 is modulated by canonical Wnt signaling, resulting in an inhibition of chondrocyte differentiation in early mesenchymal cells and directing the progenitors to become osteoblasts [8]. The process occurs during embryonic development when establishing the body axis and tissue and organ development, and it functions after birth in bone maintenance and repair [7][9]. In fact, agents that are known to activate the β-catenin pathway are used to accelerate bone healing. Sclerostin was shown to suppress bone formation, and romosozumab, an antisclerostin antibody, was approved for the treatment of osteoporosis in postmenopausal women at high risk of bone fractures [10].

On the other hand, the Wnt pathway has a key role for the development and maintenance of healthy vasculature [2]. Therefore, complications involving Wnt pathway disturbances may result in impaired vascularization. Dysregulation of components of the Wnt canonical pathway generate cardiovascular inflammatory damage, alter cellular plasticity, cause intracellular cholesterol accumulation, and lead to osteofibrotic responses [11]. There is accumulating evidence for a contribution of Wnt signaling pathways in atherosclerosis and vascular aging [5]. For example, vascular smooth muscle cells (VSMCs), which line the arterial wall and function to maintain blood pressure, are hypothesized to undergo a phenotypic switch into bone-forming cells during calcification [7]. The buildup of hydroxyapatite within the arterial wall or vascular calcification, is one of the greatest contributors to vascular disease [7]. Furthermore, the angiogenic activity of endothelial cells (ECs) is influenced by Wnt signaling. Endothelial dysfunction is the earliest and most fundamental pathological change in diabetes. Wnt, Frizzled (Fzd), and follistatin-related protein (FRP) genes are expressed by ECs and VSMCs; β-catenin is stabilized in the neovascular endothelium and neointimal smooth muscle. Activation of the Wnt signaling pathway can lead to vessel remodeling, while inhibition of Wnt signaling can lead to vessel regression. In fact, the activation of the Wnt/β-catenin signaling pathway by the administration of aFGF alleviates diabetic endothelial dysfunction [12]. Recombinant human aFGF would be an effective treatment of diabetic vascular complications due to its intervention in the Wnt pathway [12].

In addition, Wnt signaling plays an important role in the progression of heart disease, both in metabolic alterations (insulin sensitivity) and in cardiovascular remodeling and structural changes (fibrosis, sclerosis, atheroma formation, and VSMC proliferation and hypertrophy) [11]. Accordingly, the modification of components of Wnt signaling pathway is a possible therapeutic strategy to treat vasculature-related diseases.
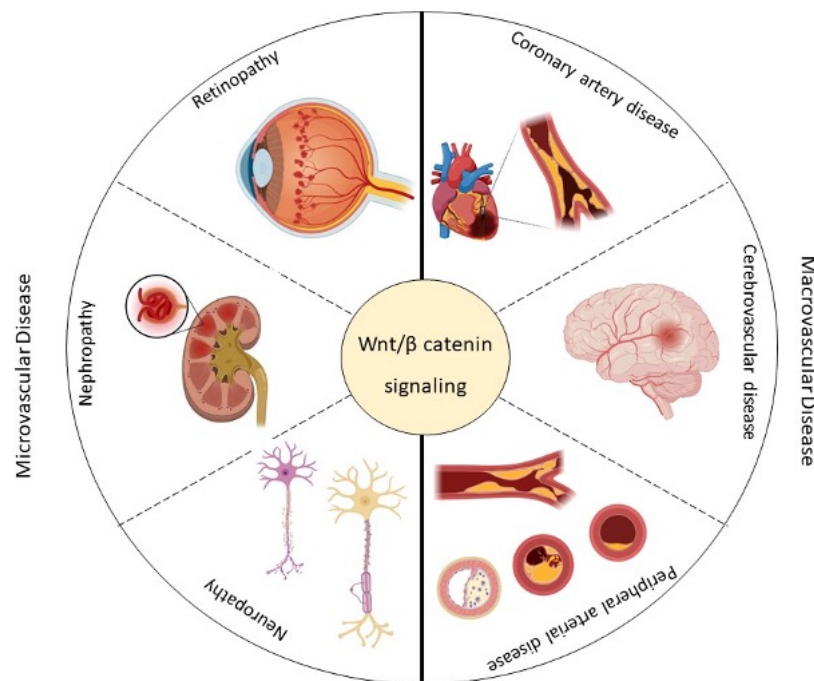
Agreeing with this evidence, several drugs targeting Wnt signaling have been shown to have a positive effect in the treatment of some vascular disorders, e.g., *Salvia miltiorrhiza* [13], recombinant human aFGF [12], and liraglutide [14].

Both canonical Wnt signaling and noncanonical Wnt signaling influence the phenotypic modulation of VSMCs in cardiovascular disease (CVD).

2. Wnt Pathway and Microvascular Disease in Type 2 Diabetes Mellitus

Patients with T2DM usually present complications related to the deterioration of the vascular system which are classified as microvascular disease when it affects small vessels [15]. The microcirculation is a network of blood vessels <150 μm in diameter, comprising arterioles, capillaries, and venules [16]. This network is responsible for the primary function of the vascular tree and regulation of tissue perfusion for optimal exchange of gases and removal of metabolic waste products, and it may contribute to the unexplained variance in the association between T2DM and hypertension [15]. Small arterioles and capillaries also exhibit differential vascular remodeling in response to hypertension and T2DM [16]. The number of vessels perfused in the vascular bed and the arteriolar diameter determine the peripheral vascular resistance [17].

The main manifestations of the microvascular disease related to T2DM are diabetic retinopathy, diabetic nephropathy, and diabetic neuropathy [18] (**Figure 2**). The mechanisms that lead to vascular damage are multiple and involve various alterations in signaling pathways, including the Wnt pathway [13][19].

Figure 2. This scheme summarizes the micro- (retinopathy, nephropathy, and neuropathy) and macrovascular (coronary artery disease, cerebrovascular disease, and peripheral arterial disease) complications associated with type 2 diabetes mellitus (T2DM) and their possible association with the Wingless-Int (Wnt) signaling pathway. Created with BioRender.com.

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The main manifestations of the microvascular disease related to T2DM are diabetic retinopathy, diabetic nephropathy, and diabetic neuropathy [18] (**Figure 2**). The mechanisms that lead to vascular damage are multiple and involve various alterations in signaling pathways, including the Wnt pathway [13][19]. **Table 1** shows some components of the Wnt pathway that are altered in the microvascular diseases in T2DM patients.

Table 1. Components of the Wnt pathway that can be altered in the microvascular complications of T2DM.[1]

Disease	Event	Component	Expression	In Vitro	In Vivo	Reference
Microvascular		β-catenin	↑	Inflammation and angiogenesis	Retinal inflammation and vascular leakage	[20]
			↑	Inflammation and angiogenesis	Retinal inflammation and vascular leakage	[20]
		LRP5/6	↓	Lack of deeper retinal vessels	Significant decrease in pathological retinal neovascularization Significant decrease in retinal vascularization during development Affects blood–retinal barrier formation	[21]
		Dkk1	↑	Inhibition of the generation of reactive oxygen species (ROS)	Mitigated retinal inflammation and blocked overexpression of proinflammatory factors such as ICAM-1 and COX-2 Reduction in retinal vascular leakage and improvement of ischemia-induced retinal neovascularization	[20]
		Frizzled4	↑	Angiogenesis	Pathological neovascularization	[21]
		Dvl2	↓	Impaired angiogenesis	Significant decrease in pathological retinal neovascularization	[21]
	Retinopathy	Claudin-5	↓	Significant suppression of endothelial cell sprouting	Suppression of pathological vascular growth and development	[21]
		Frizzled7	↑	Inflammation, angiogenesis, and oxidative stress	Pathological neovascularization	[22]
		SERPINA3K	↑	Inhibition of connective tissue growth factor overexpression	Antioxidation Anti-inflammatory Antifibrosis	[23]
		VLDLR	↑	Anti-angiogenesis Inhibited endothelial cell proliferation, migration, and tube formation	Improvement of ocular neovascularization,	[24]
		Endostatin	↑	Impaired angiogenesis	Reduced VEGF-induced retinal vascular permeability, neovascularization, and retinal detachment	[25]
		Kallistatin	↑	Anti-inflammation Anti-angiogenesis	Attenuation of ischemia-induced retinal neovascularization	[26]
		PEDF	↑	Anti-inflammation Anti-angiogenesis	Ameliorated retinal inflammation, vascular leakage, and neovascularization	[27]
		MiARN-184	↑	Anti-angiogenesis	Improves inflammatory responses, vascular leakage, and neovascularization.	[28]

Disease	Event	Component	Expression	In Vitro	In Vivo	Reference
	Nephropathy	β-catenin	↑	Reduced mesangial cell apoptosis Podocyte dysfunction	Glomerular albuminuria and subsequent glomerular injury	[29]
			↓	Mesangial cells apoptosis	Increased severity of streptozotocin-induced diabetes nephritis	[29]
		LEF1	↑	Enhanced proliferation and metastasis of renal cells	Renal cell carcinoma (RCC)	[30]
		LRP6	↓	Mesangial cell apoptosis	Attenuated renal inflammation, reduced proteinuria, and ameliorated fibrosis	[31]
		Wnt4	↑	Stimulation of mesenchymal-to-epithelial differentiation Podocyte dysfunction	Tubulo-interstitial fibrosis Glomerular albuminuria and subsequent glomerular injury	[29]
			↓	Mesangial cell apoptosis	Kidney tissue disorganization, as well as disease development and progression	[32]
		Dkk1	↑	Amelioration of podocyte apoptosis and viability	Restored podocyte function and decreased albuminuriaBone-mineral disorder syndrome	[29][33]
		TRPC6	↑	Podocyte injury	Excessive calcium influx in podocytes leading to foot process effacement, podocyte apoptosis, and subsequent glomerular damage	[29]
		Wnt9a	↑	Evoking of cell communication between senescent tubular cells and interstitial fibroblasts	Tubular senescence and renal fibrosis	[34]
		Wnt5a	↑	Increased ROS production	Mesangial cell apoptosis	[35]
		CTGF/CCN2	↑	LRP6 phosphorylation and accumulation of β-catenin	Attenuated renal inflammation, reduced proteinuria, and ameliorated fibrosis Mesangial cell apoptosis	[31]
		CTNNB1	↓	Improved podocyte motility	Damage to the basement membrane, albuminuria, and increased susceptibility to glomerular injury	[35]
		Wnt6	↓	Damaged tubulo-interstitium	Renal fibrosis	[36]

Disease	Event	Component	Expression	In Vitro	In Vivo	Reference
	Neuropathy	PORCN	↓	**Slightly reduced expression of Wnt3a Significantly reduced expression of β-catenin, Dvl1, c-myc, GRP78, and MMP2 in the sciatic nerve**	**Decreased heat- and cold-induced hyperalgesia Increased motor nerve conduction speed Increased sensory nerve conduction speed Increased nerve blood flow Increased density of intraepidermal nerve fibers**	[37]
		Dvl	↓	**Significantly reduced expression of β-catenin, Dvl1, c-myc, GRP78, and MMP2 in the sciatic nerve**	**Decreased heat- and cold-induced hyperalgesia Increased motor nerve conduction speed Increased sensory nerve conduction speed Increased nerve blood flow Increased density of intraepidermal nerve fibers**	[37]
		β-catenin	↓	**Significantly reduced expression of β-catenin, Dvl1, c-myc, GRP78, and MMP2 in the sciatic nerve**	**Decreased heat- and cold-induced hyperalgesia Increased motor nerve conduction speed Increased sensory nerve conduction speed Increased nerve blood flow Increased density of intraepidermal nerve fibers**	[37]
		Wnt3a	↑	**Release of brain-derived neurotrophic factor in microglial cells**	**Allodynia**	[38]
		XAV939	↑	**-**	**Effective attenuation of neuropathic pain induction Drastic attenuation of the development of allodynia**	[38]

[1] LRP: LDL receptor-related protein; Dkk: Dickkopf; ROS: reactive oxygen species; ICAM: intercellular adhesion molecule; COX: cyclooxygenase; Fzd: Frizzled; Dvl: Disheveled; VLDLR: very-low-density lipoprotein receptor; VEGF: vascular endothelial growth factor; PEDF: pigment epithelium-derived factor; LEF: lymphoid enhancer factor; Wnt: Wingless-Int; TRPC: transient receptor potential canonical; CTGF/CCN2: connective-tissue growth factor; CTNNB: β-catenin gene; PORCN: Porcupine; GRP78: glucose-regulated protein; MMP: matrix metalloproteinase; ↑: upregulation; ↓: downregulation.

[2] Dkk: Dickkopf; LRP: LDL receptor-related protein; LDL: low-density lipoprotein; Wnt: Wingless-Int; GM-CSF: granulocyte macrophage-colony

4. Wnt Pathway and Macrovascular Disease in Type 2 Diabetes Mellitus

Macrovascular complications are the leading cause of morbidity and mortality in patients with T2DM worldwide. Macrovascular disease includes CAD, CVD, and PAD [39]. At least 65% of T2DM patients die with some form of heart or CD, and the frequency of cardiovascular death in T2DM adults is 2–4 times higher than in their nondiabetic counterparts [40].

Activation of the Wnt pathway is critical for the induction of vascular injury, which regulates VSMC proliferation and apoptosis [41]. In addition, the Wnt signaling pathway plays a role in regulating inflammation in vessels, inducing endothelial cell proliferation and survival, and enhancing monocyte adhesion and trans-endothelial migration [42]. These pathways also play a key role in angiogenesis [43]. It is, therefore, important to maintain the stability of the Wnt pathway in the vessels. **Table 2** shows components of the Wnt pathway that are altered during the macrovascular complications of T2DM.

Table 2. Components of the Wnt pathway that can be altered in the macrovascular complications of T2DM [2].

Disease	Event	Component	Expression	In Vitro	In Vivo	Reference
Macrovascular						
		Scl	↑	Endothelial dysfunction, alteration on proliferation, and migration of vascular smooth muscle cells	Atherosclerotic process, abnormal intima-media thickness, carotid plaques, aortic calcifications, and mortality	[44][45]
			↑	Regulates platelet-mediated inflammation and contributes to plaque de-escalation	Ischemic stroke and cardiovascular death	[46]
		Dkk-1	↑	Endothelial activation and release of inflammatory cytokines Endothelial–mesenchymal transition in aortic endothelial cells	Onset and progression of atherosclerosis	[47]
		LRP6	↓	LDL uptake was significantly lower in lymphoblastoid cells	Elevated plasma cholesterol and elevated plasma LDL, triglyceride, and fatty liver levels	[48]
	Coronary artery disease	**Wnt5a**	↑	Induction of inflammatory gene expression GM-CSF, IL-1a, IL-3, IL-5, IL-6, IL-7, IL-8, CCL2, CCL8, and COX-2 in human aortic endothelial cells	Elevation of triglyceride levels, vascular insulin resistance, and endothelial dysfunction	[49]
			↑	Macrophage activation	Increased recruitment of inflammatory cells and amplified inflammatory response	[50]
			↓	Increased intima-media thickness of the carotid artery	Delayed reendothelialization and aggravated neointima formation	[51]
		Dkk-3	↑	Induces differentiation of vascular progenitors and fibroblasts into smooth muscle cells	Larger and more vulnerable atherosclerotic lesions with more macrophages, fewer smooth muscle cells, and less extracellular matrix deposition	[52]
		TCF7L2	↓	Loss of differentiation of vascular smooth muscle cells	Medial aortic hyperplasia	[53]
		Wnt2	↑	Regulates smooth muscle cell migration	Triggers intima-media thickening	[54]
		LRP5	↓	Activation of proinflammatory genes (interferon γ, IL15, IL18, and TNF ligand superfamily 13b).	Larger aortic atherosclerotic lesions	[55]

Disease	Event	Component	Expression	In Vitro	In Vivo	Reference
		Scl	↑	Arterial calcification	Ischemic stroke caused by atherosclerotic stroke of large arteries or occlusion of small arteries	[56]
		Dkk1	↑	Biomarker for the presence of coronary atherosclerotic plaque	Carotid atherosclerosis, stable angina, and myocardial infarction Poor prognosis 1 year after ischemic stroke	[57]
		miR-150-5p	↑	Regulates the Wnt signaling pathway and participates in cell proliferation and apoptosis by downregulating p53	Inhibition of cell proliferation, colony formation, and tumor growth	[58]
			↓	CD133⁻ cells acquire a stem-cell-like phenotype	>Glioma	[59]
		β-catenin	↑	Key regulators for cadherin-mediated cell–cell adhesion	Glioma Higher degree of malignancy of the tumor	[59]
	Cerebrovascular disease	Wnt1	↓	Neuronal disappearance and increasing functional deficits	Oxidant stress and cerebral ischemia	[60]
		claudin-1	↓	Neuronal damage	Increased permeability of the blood–brain barrier, petechial hemorrhage in the brain, neuronal injury, and central nervous system inflammation	[61]
		Claudin-3	↓	Neuronal damage	Intracerebral petechial hemorrhages	[62]
		Wnt3a	↑	Alleviates neuronal apoptosis at the cellular and subcellular levels	Neuroprotection in traumatic brain injury, and ischemic stroke	[63]
		LRP6	↓	Increased expression of inflammatory genes after middle artery occlusion	Risk of ischemic stroke, larger heart attack, and severe motor deficits	[64]
		Wnt5	↑	Enhanced endothelial activation type 1 inflammatory mediator to promote endothelial activation type 2	Brain aging Inflamed atheroma plaques	[65]
		miRNA-148b	↓	Attenuates neural stem-cell proliferation and differentiation	Reduces ischemic injury and improves neurological function	[66]

Disease	Event	Component	Expression	In Vitro	In Vivo	Reference
	Peripheral arterial disease	Wnt5a	↑	Endothelial dysfunction	Increased risk of peripheral arterial occlusive disease, as well as metabolic and cardiovascular disorders	[67]
		Sfrp5	↓	Inhibition of cardiac fibroblast proliferation and migration Inflammation and myocardial injury	ST-segment elevation myocardial infarction, metabolic syndrome, and increased risk of peripheral arterial occlusive disease	[67]
		CTHRC1	↑	Synovial hyperplasia, contributes to the inflammatory microenvironment, and promotes pannus invasion through increased motility and invasion of synoviocytes	Increased risk of systemic lupus erythematosus, development of rheumatoid arthritis, and severity of the disease	[68]
		ALKBH5	↑	Reduced proliferation and migration and decreased viability in hypoxic cardiac microvascular endothelial cells	Impaired hypoxic tube formation, but not the normoxic cardiac microvascular endothelial cells	[69]

[2] Dkk: Dickkopf; LRP: LDL receptor-related protein; LDL: low-density lipoprotein; Wnt: Wingless-Int; GM-CSF: granulocyte macrophage-colony stimulating factor; IL: interleukin; CCL: collagen crosslinking; COX: cyclooxygenase; TCF: transcription factor; TNF: tumor necrosis factor; Scl: sclerostin; CD: cluster of differentiation; Sfrp: secreted Frizzled-related proteins; CTHRC: collagen triple helix; ↑: upregulation; ↓: downregulation.

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