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Insulin and Cardiovascular Health: New Insights in the Field of Coronary Heart Disease Complicated with Type 2 Diabetes

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Abstract: Insulin is currently a crucial treatment for treating type 2 diabetes and plays a significant role in improving the prognosis of patients. When patients with cardiovascular disease who also have type 2 diabetes, the all-cause mortality rate increases by approximately 1.5 times. Consequently, many patients choose insulin as a treatment method for type 2 diabetes. However, the effects and mechanisms of insulin treatment on cardiovascular disease are rarely discussed. This review systematically explores the role and mechanisms of insulin and its related receptors in the progression of cardiovascular disease in patients with both conditions. It focuses on the impact of insulin on coronary plaques, cardiovascular neogenesis, and myocardium, aiming to guide clinical treatment and improve patient outcomes.
Keywords: Insulin; Insulin receptor; IR; Coronary heart disease; Signal transduction pathway; Atherosclerotic plaque

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1. Background

Insulin is a polypeptide hormone synthesized and secreted by pancreatic β-cells. It binds to tyrosine kinase receptors on the target cell membrane and regulates glucose transport and gene expression by activating downstream signaling pathways. Currently, the harm caused by diabetes, resulting from insulin deficiency or resistance, is increasing year by year. In the United States, deaths due to diabetes account for 8% of the total number of deaths. Among these patients, the mortality rate due to complications related to cardiovascular

diseases is 7.9%. Numerous studies have demonstrated that individuals with type 2 diabetes combined with cardiovascular diseases exhibit significantly worse incidence rates and prognoses compared to non-diabetic individuals. According to statistics, these patients often present with high-risk factors such as obesity and insulin resistance [1,2]. Research indicates that patients with these risk factors experience approximately a two-fold increase in mortality from cardiovascular diseases, myocardial infarction incidence, and stroke risk, as well as a 1.5-fold increase in all-cause mortality [3]. Currently, it is understood that insulin resistance can lead to water and sodium retention in the body, peripheral vascular constriction, and promote hepatic synthesis of lipid substances, resulting in elevated triglyceride levels, increased low-density lipoprotein cholesterol, higher apolipoprotein B, and increased small dense low-density lipoprotein cholesterol. These changes ultimately contribute to atherosclerosis or heart failure [3,4]. At present, the use of exogenous insulin to control blood glucose levels in diabetic patients is recognized as a common cause of insulin resistance. The DCCT study reported that intensive insulin therapy was associated with significant metabolic abnormalities, including hypertension, increased insulin demand, and dyslipidemia. Subsequent follow-up revealed the emergence of early signs of cardiovascular disease [5]. Research has found that, for patients with cardiovascular disease and early-stage diabetes, insulin therapy can reduce the risk of stroke and hospitalization due to heart failure. However, this treatment also induces hyperinsulinemia, which has various adverse effects. For example, it can cause insulin resistance, obesity, lipid distribution disorders, and inflammation [6,7]. Therefore, the specific mechanisms by which insulin affects patients with type 2 diabetes and cardiovascular diseases, as well as its clinical impact, remain incompletely understood. This review systematically compiles existing evidence and aims to explore in depth the dual roles and potential mechanisms of insulin in the progression and prognosis of cardiovascular diseases.

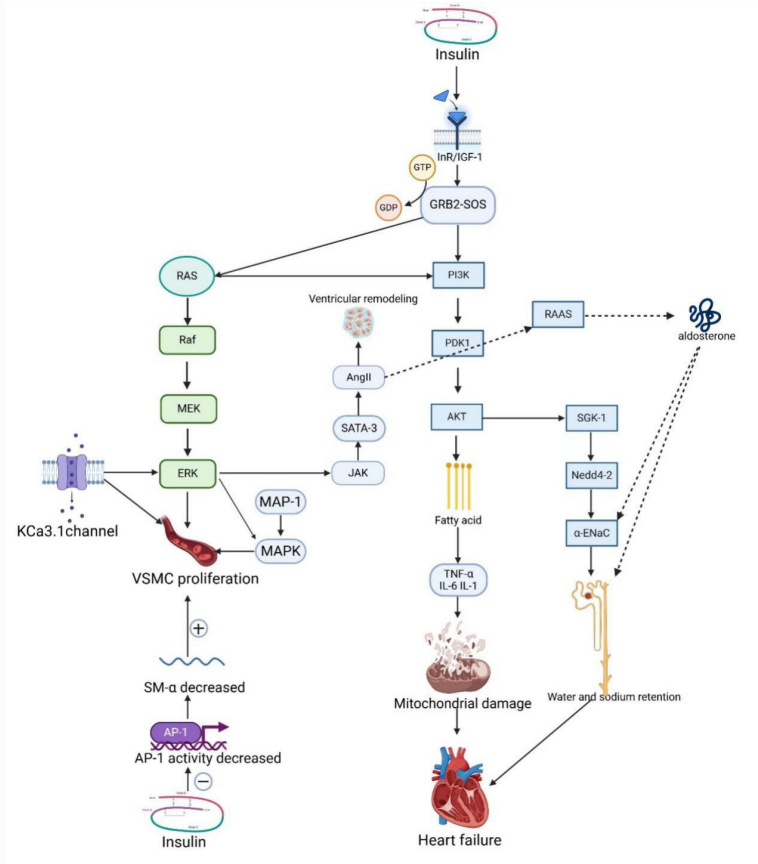

Figure 1. The specific mechanism by which insulin affects disease prognosis. InR/IGF-1: Insulin receptor/Insulin-like Growth Factor 1; VSMC: Vascular smooth muscle cells; AP-1:Activator protein-1; SM-α:Smooth Muscle Protein-α

2. Accelerate the progression of arteriosclerosis

The impact of insulin on the progression of cardiovascular diseases mainly involves influencing the formation of atherosclerotic plaques, regulating the heart muscle, promoting angiogenesis, and water and sodium retention, etc. Insulin affects the prognosis of cardiovascular diseases by influencing the activation of various signaling pathways and gene transcription (**Figure 1**).

2.1. Increased expression of adhesion molecules on endothelial cells

Coronary atherosclerotic plaques are a key feature of coronary heart disease and the primary cause of ischemic changes in the heart. Previous studies have demonstrated that the formation of these plaques is not merely due to lipid accumulation but involves ongoing inflammatory stimulation, including smooth muscle cell migration and proliferation, as well as the release of various cytokines [8]. This inflammatory response is associated with the expression of adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), on the surface of vascular endothelial cells.

Studies have shown that smooth muscle cells treated with high concentrations of insulin (10^{-9} to 10^{-7} mol/L) for 24 hours and up to 3 days exhibit increased expression of vascular cell adhesion molecule-1 (VCAM-1). Moreover, VCAM-1 expression increases further as the insulin concentration rises, reaching approximately a two-fold increase at the highest concentration [9]. Another study demonstrated that mice with defective VCAM-1 expression exhibited significantly reduced early foam cell lesions in the aorta. This finding suggests that VCAM-1 plays a crucial role in the early stages of coronary atherosclerosis, possibly by promoting monocyte aggregation in the arterial intima and thereby facilitating the formation of atherosclerotic plaques [10]. However, VCAM-1 is currently believed to be involved only in early coronary artery lesions. High levels of VCAM-1 are thought to indicate the severity of a patient's lesion or a heavy plaque burden, but there is no significant correlation with the overall risk of coronary heart disease [11].

Unlike VCAM-1, plasma levels of intercellular adhesion molecule-1 (ICAM-1) in patients with peripheral vascular disease and ischemic heart disease are significantly higher than those in healthy individuals. Moreover, plasma ICAM-1 levels in patients with acute myocardial infarction are significantly elevated compared to those in patients with chronic stable angina pectoris and healthy control subjects [12,13]. Subsequent studies have also confirmed that insulin resistance directly affects the levels of soluble cell adhesion molecules (sICAM). The authors found that the peak insulin value and the area under the insulin curve were significantly correlated with sICAM, with the strongest correlation observed for ICAM-1 ($r = 0.7$, $p < 0.001$). Additionally, there was a modest correlation with elevated postprandial triglycerides ($r = 0.29$), which is also an important risk factor for cardiovascular disease.

E-selectin, a member of the selectin family, is a cell adhesion molecule primarily involved in regulating its relatively low expression on normal vascular cells. However, its expression can be upregulated in response to various stimuli, including cytokines and oxidants, facilitating the adhesion of monocytes to the vascular wall [14]. Existing studies have shown that type 2 diabetes, an inflammatory disease, is characterized by elevated levels of E-selectin in patients. The level of E-selectin correlates with glycosylated hemoglobin levels ($r = 0.25$, $P = 0.0351$). Previous research has demonstrated that E-selectin-mediated cell adhesion plays a significant role in the early stages of coronary artery disease. E-selectin promotes the adhesion of white blood cells and vascular inflammation by binding to ligands such as sLeX. Abnormal insulin signaling can activate pathways like NF-κB, thereby enhancing E-selectin expression and increasing the production

of inflammatory factors within atherosclerotic plaques [15,16]. Furthermore, some studies have reported that although E-selectin expression increases in early-stage coronary heart disease patients, its levels are lower in unstable plaques and those with extensive calcified deposits. This suggests that during plaque progression, calcification and inflammation may reach a state of equilibrium.

2.2. Increased cell transendothelial migration

In a study [17], neutrophil migration was quantified by measuring myeloperoxidase activity, and the surface expression of endothelial adhesion molecules was assessed using enzyme immunoassay. The results demonstrated a significant enhancement in neutrophil migration across the endothelium. Furthermore, compared to healthy subjects, neutrophil migration across the endothelium was also increased in diabetic patients with hyperinsulinemia. This enhanced neutrophil migration induced by high insulin levels may contribute to the elevated incidence of atherosclerotic diseases, such as acute myocardial infarction (AMI) and stroke, in diabetic patients. Neutrophil migration appears to play a role in both the formation and destabilization of atherosclerotic plaques; for example, increased secretion of matrix metalloproteinase-9 by monocytes can weaken the fibrous cap of plaques, making them more susceptible to rupture [18].

Furthermore, this experiment demonstrated that in the high insulin group (> 50 μU/mL, for 24 hours), the migration of neutrophils across the endothelium was enhanced, which was associated with the increased expression of platelet endothelial cell adhesion molecule (PECAM-1) [17]. Under physiological conditions, although PECAM-1 can promote the adhesion and migration of white blood cells through the PI3K/Akt-FoxO1 pathway, it also has an inhibitory effect on inflammation. After the formation of atherosclerotic plaques, the PECAM-1-dependent immunosuppression is disrupted, which in turn promotes the recruitment of white blood cells and supports the atherosclerotic inflammatory response [19]. This is indeed the case. In a comparative study involving 137 patients diagnosed with coronary heart disease (with stenosis ≥ 70%) through coronary angiography and 110 healthy individuals, the levels of PECAM-1 in the plasma of patients diagnosed with coronary heart disease were significantly elevated ($r = 0.314$, $P = 0.006$), but there was no significant correlation between the number of affected vessels, and only a weak correlation with TG, LDL-C, and HDL-C[20]. Another study confirmed that ICAM-1, which is also a cell adhesion factor, plays a role in promoting the transendothelial migration of T cells. Its relationship with the migration of white blood cells is not significant. As for VCAM-1, no effect on promoting cell transendothelial migration was found [21].

The study found that in the experiment, high insulin-mediated neutrophil migration increase persisted for 72 hours, while the expression of endothelial PECAM-1 on the surface only increased within 24 hours. This indicates that the increase in neutrophil migration stimulated by high insulin in the latter 48 hours may be related to another mechanism [17]. Previous studies have noted that, in addition to PECAM-1, some intercellular junction proteins in endothelial cells, such as vascular endothelial cadherin (VE-cadherin), junctional adhesion molecule (JAM-1), CD99, and reactive oxygen species (ROS), can all affect the transendothelial migration of white blood cells [22–24]. During the following 48 hours, the migration of neutrophils increased, which might be related to this. At least for now, in individuals with insulin resistance or abnormal glucose tolerance, indicators such as VE-cadherin and ROS are significantly higher than those in healthy individuals [25].

However, in addition to the increased cell migration associated with inflammatory responses (such as neutrophils), some cells responsible for healing, such as fibroblasts and vascular endothelial cells, also

migrate to the site of myocardial injury and repair the damaged tissue. During this process, senescent fibroblasts accumulate in the myocardial infarction area, which can lead to deterioration of cardiac function. Therefore, promoting the differentiation of undifferentiated mesenchymal stem cells into new fibroblasts is an important part of restoring cardiac function. Previous studies have shown that rat mesenchymal stem cells treated with insulin-like growth factor-1 (IGF-1) can promote their differentiation into cardiomyocyte-like cells, and the presence of growth factor HGF in the cells can further enhance this effect [26,27]. Insulin and insulin-like growth factor (IGF) belong to the same insulin family and share homology in structure. Both of them are involved in cell proliferation, apoptosis, protein synthesis and metabolism, indicating that the insulin family also plays an important role in the recovery of cardiac function.

2.3. Pro-inflammatory effect

Studies have shown that in patients with insulin resistance, insulin resistance prompts macrophages to differentiate into the pro-inflammatory M1 phenotype, thereby secreting a large amount of inflammatory factors (such as TNF-α, IL-1β, IL-6, etc.) and reactive oxygen species (ROS), inhibiting the transduction of insulin-related signaling pathways and promoting the apoptosis of pancreatic β cells, forming a vicious cycle of "insulin resistance - inflammation - more severe insulin resistance" [28]. Although insulin-induced endothelial-derived Nitric oxide (NO) is an important anti-inflammatory mediator in the human body under normal conditions, in individuals with insulin resistance, the signal transduction of the PI3K/Akt pathway is impaired, resulting in reduced activation of endothelial nitric oxide synthase (eNOS) and decreased NO production. Consequently, its anti-inflammatory effect is significantly weakened [29,30]. Previous studies have shown that other inflammatory factors (such as IL-1, TNF-α) are effective inducers of VSMC proliferation. In the mouse arterial endothelial cells activated by IL-1, it was observed that VSMCs proliferated significantly and the collagen and fibrous cap decreased, indicating an increase in plaque instability and even a clear correlation with in-stent restenosis [31,32].

Studies have shown that TNF-α synthesized by macrophages in insulin-resistant patients activates the NF-κB/MAPK inflammatory signaling pathway and induces the production of matrix metalloproteinases (MMP), vascular cell adhesion molecule-1 (VCAM-1), and heparin-binding epidermal growth factor-like growth factor (HB-EGF) by endothelial cells and smooth muscle cells. These factors promote inflammatory responses and vascular dysfunction, thereby accelerating the progression of atherosclerosis (see Figure 2) [33]. In addition, the TNF-α secreted by fat cells can also phosphorylate the serine residue of IRS-1 and reduce the expression of GLUT-4, resulting in the disruption of glucose metabolism regulated by insulin and the occurrence of obesity. This study also revealed that TNF-α can trigger the inflammatory response in the body through the NF-κB/MAPK signaling pathway (a signaling pathway related to the inflammatory response) (**Figure 2**).

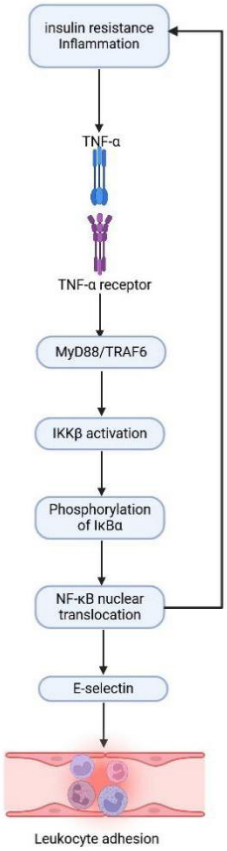

Figure 2. Relationship between TNF-α-mediated NF-κB signaling pathway and e-selectin.

2.4. The impact of reduced insulin receptors on plaques

The research has found that the reduction or absence of insulin receptor (IR) expression caused by a high-fat diet (HFD) can prompt cells to express more inflammatory factors, leading to instability of the plaques and thereby increasing the incidence of adverse events [34]. Recently, it has been discovered that the reduction in insulin receptor expression leads to the pro-atherosclerotic effect, which is associated with multiple genes. For instance, in VSMC cells with high expression of ICAM-1, genes such as Myh11, Dendritic, and Cnn1, which control myocardial contractility, were observed to be decreased, while genes related to inflammation, such as Mmp2, Mmp9, C1ra, Vcam1, Thbs1, Cc119, Tnfsf1b, and C4b, were found to be increased [35]. Other studies have also confirmed that, compared with the arteries of non-diabetic patients, the expression activity of metalloproteinase-related genes (MMP-2 and MMP-9) in the arterial endothelium of diabetic patients has increased by approximately 40% and 110%, respectively. Moreover, the degree of arteriosclerosis in diabetic patients is highly correlated with the activity of MMP-2 and MMP-9 ($r = 0.738$, $P = 0.0002$) [36]. In the analysis of the obese and metabolic syndrome population, it was found that the expression of platelet reaction protein 1 (Thbs1, a fat-derived stromal cell protein, which is considered a potential factor for obesity, insulin resistance, and the occurrence of fat inflammation) in visceral and adipose tissues was significantly increased and was correlated with body mass index ($P = 0.033$), abdominal obesity ($P < 0.001$), hyperglycemia ($P = 0.02$), and hypertension ($P = 0.04$) [37]. Compared with individuals with normal blood sugar levels, the expression of secreted frizzled-related protein 3 (Sfrp 3) in the serum of patients

with type 2 diabetes was significantly lower (0.156 ± 0.04 vs. 0.376 ± 0.07, $P < 0.05$), and it was positively correlated with the serum Sfrp3 level (r = 0.505, $P < 0.05$). Previous studies have demonstrated that the Sfrp family plays an important role in promoting the proliferation and differentiation of cardiac cells and maintaining cardiac structure. Sklepkiewicz et al. reported that long-term absence of the Sfrp1 gene could even lead to changes in heart structure [38]. However, the specific pathogenic mechanisms of some genes remain unclear, and further research is needed at present.

Additional experiments revealed that in mice with insulin receptors knocked out, the degree of aortic lipid deposition on the surface of vascular smooth muscle was approximately 90% higher than that of the control group mice ($P = 0.02$), the necrotic area of the plaque increased by 41% ($p = 0.045$), and the collagen content in the plaque decreased by 29% ($P = 0.01$). Moreover, in the rat group with insulin resistance (where insulin receptor expression was reduced), thickening of the aortic wall and disordered aortic media structure were observed (108.00 ± 20.0 mm VS 83.28 ± 12.15 mm), but no statistical differences were found in this experiment [39]. This was also observed in other studies, and it was believed that after insulin receptor activation, it might promote VSMC proliferation and migration by down-regulating the expression of p21 WAF1 through microRNA-208 and inducing dysfunction of dopamine D1 receptors, thereby thickening the aortic wall. Past studies have shown that changes in the structure of the arterial wall can serve as an independent predictor of the incidence and mortality of cardiovascular diseases (CVD). The thickness of the aortic wall is closely related to the short-term and long-term incidence and mortality of CVD. This provides further evidence that the reduced expression of insulin receptors is an important factor contributing to the increased risk of cardiovascular diseases [34].

3. Effects on the myocardium

3.1. The lipid toxicity of insulin on cardiomyocytes

Research has found that insulin has a dual effect on Cardiomyocytes: under ischemic conditions, insulin plays a crucial role in the cardiac muscle's adaptation to stress. It is particularly important in enhancing glucose metabolism, reducing the oxygen consumption of Cardiomyocytes, and inhibiting the apoptosis of Cardiomyocytes [40]. However, under long-term high insulin levels in the body, insulin continuously increases the expression of angiotensin II (Ang II) through the MEK/STAT 3 pathway, continuously activating the renin-angiotensin-aldosterone system, thereby exacerbating ventricular remodeling and myocardial lipid toxicity damage [40].

As mentioned earlier, the use of exogenous insulin leads to an increase in insulin concentration in the body. This long-term high insulin environment reduces the sensitivity of fat cells and skeletal muscle cells to insulin, thereby causing insulin resistance. However, studies have shown that cardiomyocytes remain sensitive to insulin in this high insulin environment. In a clinical trial, it was observed that the expression of the PI 3-Akt pathway in cardiomyocytes increased in patients with insulin-dependent diabetes mellitus (NIDDM), and as the expression of this signaling pathway increased, the uptake of glucose by cardiomyocytes decreased, while the uptake of fatty acids increased and gradually accumulated. This change is known as myocardial lipotoxicity [41,42]. The pathogenic mechanism includes an increase in reactive oxygen species (ROS) due to lipid overload, which leads to damage of the mitochondrial respiratory chain and a reduction in ATP production; an increase in the release of inflammatory factors (such as TNF-α)

and the induction of apoptosis in Cardiomyocytes; endoplasmic reticulum stress interferes with protein folding and calcium homeostasis, further exacerbating cell damage and insulin resistance [43–45]. Research has found that long-term exposure of Cardiomyocytes to lipid toxicity leads to cellular damage, which results in decreased contractility of Cardiomyocytes, cardiac hypertrophy, and fibrosis [46]. Furthermore, since individuals with insulin resistance often have impaired mitochondrial function, the mitochondria in Cardiomyocytes have a reduced ability to oxidize fatty acids. This undoubtedly leads to an increase in fatty acid accumulation, exacerbates mitochondrial damage, and forms a vicious cycle. This manifestation is particularly evident in patients with advanced heart failure [47]. Another survey indicates that in patients with insulin resistance, due to the increase in glucose and lipid metabolites, as well as the elevated expression of oxidants and inflammatory cytokines, the combined effect of these factors leads to an increase in de novo synthesis of diacylglycerol (DAG); DAG is an activator of protein kinase C(PKC)subtypes [48]. The activated PKC subtypes PKCβ and PKCδ enhance the activity of the IRS/1/2/PI 3 K/Akt signaling pathway and simultaneously increase the expression of mitogen-activated protein kinase (MAPK). This indicates that lipid accumulation not only affects the structure and function of the heart but also accelerates the progression of atherosclerotic plaques.

3.2. The impact of insulin on the risk of heart failure

The heart, as an insulin-dependent energy-consuming organ, insulin not only plays a crucial role in the absorption and utilization of glucose, but also supports the growth of Cardiomyocytes and the recovery of cardiac function [49].

Recent clinical studies have shown that a significant proportion of patients with heart failure have insulin resistance. Patients with insulin resistance or type 2 diabetes have approximately 1.5 to 2 times higher risk of heart failure.[50,51]. It can be seen that there is a close connection between insulin resistance and heart failure. Combined with previous studies, the possible mechanisms leading to the occurrence of heart failure are as follows: We found that insulin needs to continuously bind to IRs to inhibit the expression of the angiotensinogen gene mediated by Foxo1 and the production of Ang II, in order to lower blood pressure and maintain normal cardiac function. Therefore, in patients with insulin resistance or type 2 diabetes, the lack of utilization of insulin leads to an increase in the expression of the angiotensinogen gene mediated by Foxo1, thereby increasing the incidence of heart failure or ventricular remodeling [49,52].

Insulin can also affect the contractile function of the heart muscle and hemodynamics by activating Gi-biased beta 2-adrenergic signaling. After mouse cardiomyocytes are pre-treated with insulin, the Gi-beta 2 signal can effectively weaken the cAMP/PKA signal transduction in cardiomyocytes after beta-adrenergic nerve stimulation, thereby inhibiting PKA phosphorylation and the contraction response of cardiomyocytes, and ultimately leading to cardiovascular dysfunction. In the study, they believe that heart failure is a manifestation of insulin resistance or hyperinsulinemia [53,54].

Therefore, some researchers believe that for patients with heart failure and insulin resistance, compared to the sole use of insulin, the combined application of GLP-1 receptor agonists, SGLT2 inhibitors, ACEI/ARB drugs, etc., can reduce the incidence of adverse cardiovascular events in these patients [55,56].

3.3. Water-sodium retention

The occurrence of cardiovascular adverse events in patients receiving insulin treatment is related to its

characteristic of causing water and sodium retention in the patient's body. Currently, it is believed that insulin activates corresponding signaling pathways (such as PI3K/Akt), which leads to the expression and phosphorylation of α-ENaC (one of the subunits of epithelial sodium channels), enhancing the reabsorption capacity of sodium in renal tubules and resulting in water and sodium retention. Additionally, insulin can enhance the effect of aldosterone on α-ENaC, reducing the excretion of water and sodium. This is particularly significant in patients with hyperinsulinemia and type 2 diabetes [57]. In the study by Vicent et al., the rehospitalization rate due to heart failure within one year for patients with heart failure who received treatment for type 2 diabetes was evaluated. The results showed that the risk of rehospitalization due to HF within one year for patients receiving treatment for type 2 diabetes was significantly higher than that for diabetic patients who did not receive insulin treatment (risk ratio 1.28; $P < 0.022$) [58]. Another European clinical trial demonstrated that patients with HF who received insulin treatment had significantly increased risks of all-cause mortality (OR: 2.02) and re-hospitalization due to HF (OR: 1.42), and their usage rate of loop diuretics was also significantly higher than that of the control group [59]. Loop diuretics are also an important factor influencing the prognosis of heart failure [60]. It is worth noting that patients using SGLT-2 inhibitors had a significantly lower mortality rate from heart failure compared to the control group (5.7% vs 8.5%, HR: 0.66, $P < 0.001$), and the usage rate of loop diuretics was also relatively lower. This suggests that, on the basis of ensuring good glycemic control, SGLT-2 inhibitors may be a more preferable choice [61].

4. The impact of angiogenesis

4.1. Stimulate the proliferation of vascular smooth muscle cells

The proliferation of human arterial smooth muscle cells can be stimulated by insulin in the plasma, indicating that insulin is a serum growth factor that can stimulate the proliferation of smooth muscle cells in the vascular wall [62]. In a study conducted on spontaneously hypertensive rats (SHR), it was found that insulin, under conditions of high insulinemia or hypertension in the rats, causes an impairment in MKP-1-induced signaling, leading to an increase in signal transduction of the MAPK signaling pathway. This results in differential stimulation of the mitosis of vascular smooth muscle cells (VSMCs), thereby promoting the proliferation of vascular smooth muscle cells in the rats [63]. However, insulin not only promotes the proliferation of VSMCs through the MAPK pathway, but also the ERK 1/2 pathway and the KCa 3.1 pathway can all promote the proliferation of VSMCs under the influence of insulin [64]. The ERK 1/2 pathway is located downstream of IGF-1 in the signal cascade that affects cell proliferation. Since insulin and IGF-1, as well as insulin receptors and IGF-1R, all have considerable homology and structural similarities, high concentrations of insulin can additionally bind to IGF-1R, activating IGF-1 and subsequently activating ERK1/2, thereby promoting the proliferation of VSMCs [65]. In this study, it was also confirmed that the phosphorylation level of ERK 1/2 increased after insulin treatment (compared with the control group, the phosphorylation degree of the ERK1/2 pathway increased by 35%, $n = 5$, $P < 0.01$) [64]. Recent studies have shown that in addition to the MAPK signaling pathway, insulin also promotes the proliferation of vascular smooth muscle cells through the transcriptional activator protein (activator protein-1, AP-1) and smooth muscle-microfilament alpha (SM-α) signaling pathways. In this study, different concentrations of insulin were added to the culture of rat VSMCs, and the results showed that the expression of AP-1 and SM-α in rat VSMCs stimulated by insulin significantly decreased (decreased by more than 50% compared to the blank control) [66]. Previous studies have shown that rats without SM-α expression died within 1-9 days after birth due to abnormal proliferation

function of VSMCs. Another study indicated that in patients with high-risk factors for coronary heart disease (such as high cholesterol levels, vascular endothelial damage, atherosclerotic plaque formation, etc.), the expression of SM22-α in VSMCs was also significantly reduced [67].

Studies have shown that insulin receptor (IR)-negative microvessels consistently display clear expression of type IV collagen. Generally, the expression of type IV collagen indicates the maturation of vascular endothelium. This suggests that the presence of IR may stimulate the formation of new blood vessels within coronary plaques [68,69]. OTUD 6B, as a member of the functional deubiquitinating protease subfamily that encodes ovarian tumor domains, plays a significant role in regulating cell proliferation, migration, and other cellular processes. OTUD6B can arrest cells in the G1 phase to inhibit cell proliferation. In the experiment, the author used a mouse model of diabetes-induced atherosclerosis. The results showed that the expression of OTUD6B in diabetic atherosclerosis patients was significantly decreased, thereby promoting the growth of new blood vessels in the coronary artery and reducing the stability of atherosclerotic plaques [70]. A7r5 cells are fibroblasts derived from the smooth muscle of the thoracic aorta of rat embryos. In a recent study, it was discovered that at a concentration of 10 μM (the optimal concentration that can induce proliferation of rat aortic smooth muscle cells) [71]. After 24, 48, and 72 hours of insulin treatment, the proliferation rates of A7r5 cells were 223.38%, 235.71%, and 192.01% of the control group (without insulin treatment), respectively. It can be seen that the proliferation rate of A7r5 cells significantly increased after insulin treatment. This process involved changes in the expression of multiple genes, such as Myc, Jun, Ccnd1, etc., which are involved in the positive regulation of cell proliferation and the regulation of the cell cycle [72].

4.2. Promoting angiogenesis effect

Insulin and insulin-like growth factor (IGF) belong to the same insulin family and share homology in structure. Therefore, both of them are involved in cell proliferation, apoptosis, protein synthesis, and metabolism. The angiogenic effect of IGF-1 plays a crucial role in preventing CVD from progressing to MI. The rapid formation of microvessels has the potential to rescue ischemic myocardium in the early stage of MI, thereby avoiding impairment of cardiac function [73]. Studies have shown that in vascular endothelial cells treated with IGF-1, the formation of microvessels is accelerated compared to before, and the expression of angiogenesis-related genes and proteins in endothelial cells is upregulated. According to the research, the activation of the PI 3 K/Akt signaling pathway plays an important role in this process [74]. Although no studies have yet demonstrated that insulin has a direct role in promoting angiogenesis, insulin shares homology with IGF and can bind to the receptors of IGF to a certain extent. Moreover, some research has indicated that in a normal physiological concentration of insulin environment, insulin can activate the relevant signaling pathways of vascular endothelial cells and vascular smooth muscle cells, thereby upregulating the expression of angiogenic factors (VEGF). And VEGF has been proven to play an important role in the formation of collateral circulation in coronary arteries [75]. Therefore, this article suggests that insulin can, to some extent, promote the regeneration of coronary blood vessels. Moreover, in patients with non-ST-segment elevation myocardial infarction (NSTEMI), the vasodilatory effect of insulin can reduce ischemia by either increasing the blood flow in partially blocked culprit vessels or by enhancing collateral blood flow, which also facilitates the establishment of subsequent collateral circulation [76].

However, the angiogenic effect of insulin only takes effect at normal physiological concentrations. In patients with type 2 diabetes or IR, due to the high insulin environment in the body, the formation of

coronary collateral vessels is observed to be reduced instead. The main reasons for this may be the decreased bioavailability of nitric oxide, increased expression of endothelin-1 and adhesion molecules, intensified oxidative stress, and increased vascular permeability. Furthermore, cystatin C, as an endogenous anti-angiogenic factor, a large cohort study involving 866 patients with coronary heart disease showed that 57% (n = 498) of type 2 diabetic patients had a significant correlation between the inhibition of coronary artery collateral formation and elevated cystatin C levels. Therefore, when evaluating the prognosis of diabetic patients with cardiovascular diseases, the increase in cystatin C is an important predictor of poor prognosis for the patients [77].

4.3. Vascular proliferation within the plaque

Studies have shown that after being treated with insulin, the capillary-like vessels within the microvascular endothelial cells of the human body significantly increase in formation, thereby leading to the formation of new microvessels within the plaque. An increase in vascular density within the plaque significantly increases the incidence of perioperative adverse events (7.1% vs 3.8%, 95% CI), and compared with healthy patients, the risk of adverse events within 3 years is significantly higher (30% vs 23.8%, HR = 1.4) [78]. The mechanism may be that after the microvascular density within the plaque increases, it becomes easier for the blood vessels to dilate. After dilation, the white blood cells in the blood vessels are more likely to be released into the plaque, triggering an inflammatory response within the plaque (such as the release of proteolytic enzymes and an increase in plaque matrix breakdown), thereby making the plaque no longer stable [79]. Furthermore, insulin itself can also cause adverse changes such as angiogenesis through its binding to its own receptors.

5. Conclusion

On the one hand, insulin exacerbates the progression of atherosclerosis by activating various signaling pathways, thereby increasing the risk of cardiovascular events. On the other hand, at physiological concentrations, insulin has a protective effect on cardiomyocytes. Therefore, in clinical practice, when formulating treatment strategies for type 2 diabetes combined with cardiovascular diseases, the impact of insulin on metabolism and cardiovascular function should be comprehensively considered. It is not advisable to rely solely on insulin treatment; instead, drugs with cardiovascular protective effects should be combined to achieve more comprehensive control of metabolic and cardiovascular risks. Further research is needed to understand how insulin affects the expression of related genes through signaling pathways, in order to provide new targets and strategies for precise treatment of diabetes-related cardiovascular diseases.

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Disclosure statement

The authors declare no conflict of interest.

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