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The potential of adipokines as biomarkers and therapeutic agents for vascular complications in type 2 diabetes mellitus

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ABSTRACT

Over the past decades, there has been a major increase in type 2 diabetes (T2D) prevalence in most regions of the world. Diabetic patients are more prone to cardiovascular complications. Accumulating evidence suggests that adipose tissue is not simply an energy storage tissue but it also functions as a secretory tissue producing a variety of bioactive substances, also referred to as adipokines. The balance between pro-inflammatory adipokines and protective adipokines is disturbed in type 2 diabetes, this can be regarded as adipose tissue dysfunction which partly promote the pathogenesis of diabetes complications. In this review, we not only discuss the favorable adipokines like adiponectin, omentin, C1q tumor necrosis factor-related proteins, but also unfavorable ones like resisitin and visfatin, in the aim of finding potential biomarkers recommended for the clinical use in the diagnosis, prognosis and follow up of patients with T2D at high risk of developing cardiovascular diseases as well as leading to new therapeutic approaches.

1. Introduction

Adipose tissue has been traditionally considered as a passive reservoir for energy storage. But with the discovery of several molecules secreted from adipose tissue, our understanding of the role and the complexity of adipose tissue has changed greatly. Adipokines not only regulate lipid metabolism but also function in a wide array of physiological or pathological processes as diverse as host defense, inflammation, apoptosis, autoimmunity, cell differentiation, and organogenesis [1–5]. The first adipokine, leptin, was discovered in 1994 [6]. Since then, a series of adipokines were discovered, which aroused great interest of scholars, especially adiponectin, C1q/ tumor necrosis factor (TNF) related proteins (CTRPs), visfatin, vaspin, chemerin, and omentin. Furthermore, the adipose tissue is also being regarded as a source of proinflammatory mediators which contribute to vascular injury, insulin resistance and cardiovascular disorders. the adipokines, as known nowadays, include: tumor necrosis factor-α(TNF-α), Interleukin-6 (IL-6), leptin, plasminogen activator inhibitor 1 (PAI)-1, angiotensinogen, resistin, monocyte chemoattractant protein-1 (MCP-1) and C-reactive protein (CRP). Some of them have a protective role against vascular inflammation and insulin resistance, namely: the adiponectin, omentin, parts of CTRPs and the nitric oxide [7,8]. Those adipokines like adiponectin, CTRP3, CTRP9, CTRP13 are further downregulated in diabetes patients with cardiovascular disease which link metabolic disorders and atherosclerotic CVDs. Thus, these adipokines may have potential as biomarkers and therapeutic agents for cardiovascular disease in diabetes patients.

2. Adiponectin

Adiponectin was identified by Scherer, P.E et al in the mid-1990s. which has 4 distinct domains, an N-terminal signal peptide, a variable domain, a collagenous domain and a C-terminal C1q-like globular domain. Adiponectin consists of 244 amino acids [9] and is located on chromosome 3q27 [10], a region associated with type 2 diabetes and CVD [11]. Adiponectin is synthesized primarily in white adipose as a

Abbreviations: CAD, coronary artery disease; T2D, Type 2 Diabetes Mellitus; CTRP, C1q/ tumor necrosis factor (TNF) related protein; HAN, high molecular weight adiponectin; TNF-α, tumor necrosis factor-α; IL-6, Interleukin-6; PAI-1, plasminogen activator inhibitor 1; MCP-1, monocyte chemoattractant protein-1; CCL2, chemokine C-C motif ligand 2; CRP, C-reactive Protein; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1; MACE, major adverse cardiovascular events; FMD, high-resolution ultrasound of the brachial artery; MMP, matrix metalloproteinase; NF-κB, nuclear factor-κB; AMI, acute myocardial infarction; ED, endothelial dysfunction; PAD, peripheral arterial disease; BMS, bare metal stent; HAN, high molecular weightadiponectin

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monomer. In healthy individuals, circulating adiponectin is normally between 5–30 u g/ml and is lower in individuals with adiposity, insulin resistance and type 2 diabetes [12–14].Numerous epidemiological studies suggest that adiponectin deficiency is associated with coronary artery disease and hypertension [15,16]. Besides, increasing evidence from experimental studies indicates that adiponectin plays a crucial role in preventing metabolic and cardiovascular disease [17]. Thus, it is likely that adiponectin represents a hyperglycemic state, and clarifies the pathogenesis of diabetes-linked cardiovascular disorders.

2.1. Hypoadiponectinemia - an additional CVD risk factor in T2D

Many clinical studies have shown that hypoadiponectinemia is associated with endothelial dysfunction, greater carotid intima-media thickness(IMT), and coronary artery disease [18,19]. In vascular levels, actions of the adiponectin comprise reduction in expression of intercellular adhesion molecule-1(ICAM-1), vascular cell adhesion molecule-1(VCAM-1) and E-selectin. They also inhibit the transformation of macrophages into foam cells and the proliferation and migration of smooth muscle cells which have a protective effect on atherosclerosis [20]. Thus, low serum adiponectin level is now considered a CVD risk factor, type 2 diabetic patients with low concentrations of this protein would have increased risk of developing premature arteriosclerosis. In other words, lower levels of serum adiponectin is an additional CVD risk factor for the patients with type 2 diabetes [21]. To date, the links between T2D and the development of cardiovascular disease have been studied at the molecular and genetic level. Several studies have indicated the role of adiponectin gene variants in the increased coronary artery disease (CAD) risk in T2D patients. Al-Daghri NM, et al examined the association of SNP45T > G and SNP276G > T of adiponectin gene with CAD risk in T2D patients in a Saudi population and find out that The SNP45T > G was significantly associated with risk of CAD but not SNP276G > T. The association of SNP45T > G with CAD risk remained significant even after adjusting for potential confounding factors. These findings support a role for adiponectin gene variants in the increased CAD risk in diabetes patients [22].

Interestingly, Wei-Chin Hung et al find out that diabetic patients with high-plasma adiponectin levels have higher major adverse cardiovascular events (MACE) rates than those with low-plasma adiponectin levels. They also concluded that high adiponectin plasma concentrations can independently be associated with MACE in CAD with T2DM but not in those without diabetes [23]. These finding runs contrary to the fact that plasma adiponectin levels were lower in patients with T2DM and CAD. But this study is based on the type 2 diabetic patients with coronary artery disease, it can be explained that adiponectin synthesis is stimulated in response to vascular inflammation to counter the atherosclerotic process [24]. Hence, according to this issuer, adiponectin indicates an increased risk of cardiovascular disease and mortality that seems to be related to the severity of the disease. Fujita T et al. simultaneously indicated that circulating high molecular weight adiponectin (HAN) reflects the pathophysiological state of insulin resistance and renal involvement in T2DM [25]. Jiang W. et al. draw a conclusion that after adjustment of conventional atherosclerosis risk factors, adiponectin was negatively correlated with the severity of peripheral arterial disease. This study indicates that adiponectin may be a marker for evaluating peripheral vascular lesions of type 2 diabetes mellitus [26]. Inconclusion, adiponectin can be used to evaluate the risk of severity of cardiovascular disease and peripheral vascular complications in asymptomatic diabetic patients.

2.2. Increasing circulatory adiponectin- therapeutic strategy

Clinic study proved that treatment with the thiazolidinedione (TZD) class of insulin-sensitizing drugs can increase expression and secretion of adiponectin which can significantly improves endothelial and adipose tissue dysfunction [27]. The prospective pioglitazone clinical trial in macrovascular events (PRO active) study also shows that treatment with pioglitazone (one of the TZDs) improves cardiovascular outcome in patients with type 2 diabetes [28]. Pioglitazone-induced amelioration of insulin resistance and diabetes is mediated, at least in part, through adiponectin-dependent pathway [29]. Thus, adiponectin may play crucial roles in the cardiovascular protective effects of TZDs. Moreover, fenofibrate, a peroxisome proliferator-activated receptor (PPAR)-α ligand, is widely used for the treatment of dyslipidemia clinically. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study demonstrates that fenofibrate reduces cardiovascular events in patients with type 2 diabetes [30]. Of note, in the FIELD study, fenofibrate therapy is associated with lower risk of limb amputations in patients with type 2 diabetes [31]. Therefore, the PPAR-a ligand could ameliorate angiogenic repair in ischemic limbs, at least in part, by its ability to increase adiponectin production. Considering the favorable actions of adiponectin on cardiovascular system, adiponectin can be used as a therapeutic strategy for cardiovascular complications in diabetic patients. However, up to this date, there is no recombinant adiponectin protein is practically used in clinical. Further investigations should focus on this point.

3. Resistin- promoting cardiovascular injury in patients with T2D

Resistin is a hormone specific of the adipose tissue recently discovered, which directly induces the insulin resistance in muscles and liver. The resistin induces the expression of messenger RNA producer of endothelin-1 in endothelial cells, thus contributing to endothelial dysfunction. It also significantly increases the expression of the cellular adhesion molecule VCAM-1 and the MCP-1, the factors in formation of early atherosclerotic lesion [32]. This is consistent with Verma S, who suggest resistin promote cardiovascular disease via proinflammatory pathways [33]. Serum concentrations of resistin are elevated in humans who are obese [34] as well as in patients with T2D [35]. Diabetic nephropathy has been associated with alteration of a variety of inflammatory markers, Burnett MS et al indicate that resistin is also increased in this condition [36]. Moreover, diabetic nephropathy is an important predictor of later cardiovascular disease in this population [37].

It was recently demonstrated the proinflammatory action of resistin in smooth muscle cells: it induces the proliferation of such cells, suggesting the action of these hormones is restenosis of coronary lesions in patients with diabetes [38]. On YK et al reported that serum resistin concentrations were higher in type 2 diabetic patients with CAD (DMCAD), compared with the concentrations in diabetics patients without CAD (diabetes mellitus, DM), and the pre-procedural serum resistin concentrations were higher in type 2 DM patients with restenosis after stenting with a bare metal stent (BMS) than in those who did not experience restenosis [39]. Serum resistin might be a biological marker for developing cardiovascular disease in patients with T2D and restenosis after stenting with a bare metal stent. The following areas required further investigation: (i) the mechanism of resistin in the development of atherosclerosis in patients with type2 DM; (ii) The therapeutic potential of resistin antibody in preventing diabetic cardiovascular complications and restenosis with bare metal stents in type 2 DM patients.

4. Omentin

Omentin was identified in an omental fat cDNA library in 2005 [40]. Unlike leptin and adiponectin that are primarily expressed in adipocytes, Omentin mRNA is present in the nonfat cells of this fat [41]. Omentin is composed of 313 amino acids, and mainly expressed in visceral adipose tissue. More specifically, it is expressed in visceral adipose stromal vascular cells, rather than in subcutaneous adipose tissue [42]. Omentin is encoded by 2 genes, omentin-1 and omentin-2, and the former is the major circulating form. In this review, we refer to

omentin-1 as omentin. Accumulating evidence indicates that the obese state is characterized by chronic low-grade inflammation and adipose tissue dysfunction, which leads to the initiation and progression of obesity-related disorders, such as T2DM, hypertension, CVD, and atherosclerosis [43]. Omentin, as a newly discovered adipokine, plays an anti-inflammatory role, as reported by several groups, which may provide a novel therapeutic target [44].

4.1. Omentin- a useful biomarker of vascular dysfunction

Previous studies in humans showed that circulating omentin levels are decreased in obesity, metabolic syndrome, and type 2 diabetes (T2D) and are inversely correlated with parameters of obesity, insulin resistance, and metabolic risk factors [45–49]. Consistent with the experimental evidence, circulating omentin levels were shown to be decreased in patients with coronary artery disease [50,51] and established carotid atherosclerosis [52]. Therefore, plasma omentin concentration may reflect vascular dysfunction to some extent, especially for diabetic patients. Moreno-Navarrete JM et al demonstrated that the circulating omentin-1 concentration independently associated with FMD (high-resolution ultrasound of the brachial artery) even after controlling for adiposity, age, and inflammation in subjects with impaired glucose tolerance, they also indicated that proinflammatory cytokines (TNF-α and IL-6) are negatively associated with circulating omentin concentrations. A plausible interpretation of these findings links the proinflammatory state of IGT subjects with decreased omentin levels resulting in impaired vascular tone [53]. Circulating omentin levels are negatively correlated with carotid intima-media thickness (IMT) in apparently healthy men and type 2 diabetic patient [54,49]. Xu T et al demonstrated that ischemic stroke patients with unstable carotid plaque had significantly lower levels of serum omentin-1 than patients with stable plaque, which indicate omentin may represent a biomarker for predicting carotid plaque instability [47]. Hye Jin Yoo, et al find out that serum omentin levels were significantly decreased in type 2 diabetes patients compared to normal glucose controls and was further reduced in type 2 diabetes patients with carotid plaque even after adjusting for age, gender, body mass index, systolic blood pressure, fasting blood glucose, low density lipoprotein cholesterol, and history of smoking and medication, they draw a conclusion that circulating omentin level was independently correlated with arterial stiffness and carotid plaque in type 2 diabetes [49]. Unfortunately, this study included a limited sample and was not representative. Interestingly, Hayashi M et al. also investigated the association between plasma omentin levels and vascular endothelial function, as assessed by FMD, in patients with T2D. they demonstrated that plasma omentin levels were positively associated with FMD, a surrogate marker for CVD, in subgroups of patients with T2D at high CVD risk, such as those with older age, renal dysfunction, or preexisting CVDs. On the contrary, no significant association was found between omentin and FMD in low-risk subgroups of patients with T2D or in non-diabetic controls. Which demonstrated that plasma omentin levels are independently associated with endothelial function in subgroups of patients with T2D at elevated cardiovascular risk. These results suggest that omentin directly promotes endothelial function in human subjects with diabetes and CVD risk factors [55]. which can be a useful biomarker of vascular dysfunction of in type 2 diabetic patients.

4.2. Omentin- plays a protective role in cardiovascular diseases

Several lines of evidence from animal studies indicate the protective effects of omentin against cardiovascular damage through its actions on vascular endothelium, smooth muscle cells, macrophages, and cardiomyocytes [56–61]. Maruyama S, et al indicated that omentin promotes endothelial cell function and revascularization in response to ischemia through its ability to stimulate an Akt-eNOS signaling pathway [56]. Kataoka Y, et al indicated that increase in circulating human omentin by adenoviral or transgenic overexpression systems before the induction of ischemia leads to a reduction of cardiac injury after reperfusion in mice through both AMP-activated protein kinase- (AMPK) and Akt-dependent mechanisms [61]. These results suggest that omentin not only serves as a valuable biomarker for cardiovascular complications but also acts as a therapeutic strategy. So, increasing circulating omentin levels may be a novel therapeutic strategy to treat cardiovascular diseases in diabetic patients. But additional experimental studies and large-scale prospective clinical studies are warranted to clarify the practical values of omentin on atherosclerotic process in people with type 2 diabetes.

5. Visfatin- an inflammatory mediator induced cardiovascular events

Visfatin is an adipocytokine that was recently identified by Fukuhara et al [62]. Which elevated in obesity, insulin resistance, type 2 diabetes mellitus, and pro-inflammatory states [63]. More recently, it has been suggested that visfatin is an inflammatory mediator, based on its localization in macrophages within atherosclerotic lesion and its ability to induce matrix metalloproteinase (MMP)-9 in monocytes [64]. The role of visfatin as mediator of inflammatory is reaffirmed by Adya R et al. They also indicated that visfatin significantly increased nuclear factor-κB(NF-κB), a well-known proinflammatory transcription factor, transcriptional activity in human endothelial cells which might affects the activation of gelatinases MMP-2 and -9, In that way might lead to atherosclerotic plaque instability [65]. Visfatin has previously been indirectly linked to atherogenesis through its effects on glucose homeostasis [66]. Takebayashi K et al showed that visfatin is negatively associated with vascular endothelial function (evaluated by FMD) in diabetic patients [67].

Additionally, it is well documented that visfatin is involved in endothelial dysfunction (ED), which causes progression of atherosclerosis and therefore plays an important role in different forms of cardiovascular diseases [68]. Mazaherioun M et al have detected visfatin levels were significantly higher in acute myocardial infarction (AMI) patients that have shown visfatin could contribute to atherosclerosis and plaque destabilization which in turn, leads to myocardial infarction. They also have shown that a visfatin level > 7.244 ng/ml had a sensitivity of 70% and a specificity of 75% for detecting patients with AMI [69]. We can draw a conclusion that visfatin plays an important role in the pathogenesis of vascular inflammation in type 2 diabetes, it is tempting to hypothesize that this adipokine could contribute to the inflammatory state and increased risk for cardiovascular events characterizing patients with type 2 diabetes in a direct way rather than diabetes itself. The specific mechanism needs to be further explored.

6. C1q tumor necrosis factor-related proteins (CTRPs)

C1q tumor necrosis factor-related proteins (CTRPs) are members of the highly conserved family of adiponectin, and all of these proteins share the same modular organization as adiponectin, consisting of a signal peptide, a short variable region, a collagen domain and a globular C1q domain [70]. There are 15 members ranging from CTRP1 to CTRP15 with related structures and diverse functions [71]. Unlike the adiponectin transcript, which is expressed almost exclusively by adipocytes [72] CTRPs are widely expressed in human and mouse tissues [73]. Although adipose tissue predominantly expresses CTRP1, CTRP2, CTRP3, CTRP5, CTRP7, CTRP9, CTRP12, and CTRP13, each CTRP shows a unique tissue expression profile that may reflect unique functions. [73–76].In this review, we mainly explore the relationship between serum CTRP1、CTRP3、CTRP9、CTRP13 levels in patients with type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) (Fig. 1).

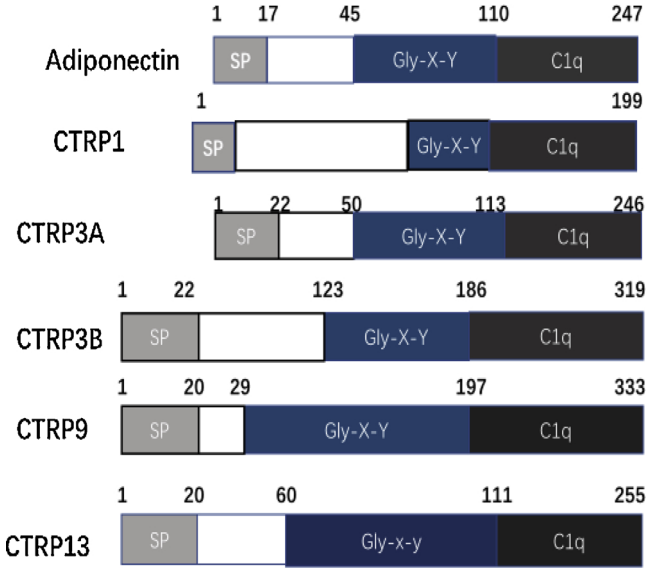

Fig. 1. Schematic of adiponectin, CTRP1, CTRP3, CTRP9, CTRP13. These factors contain four domains: a signal peptide for secretion (light gray), an N-terminal domain with one or more conserved Cys residues (white), a collagen domain with varying numbers of Gly-X-Y repeats (blue), and a C-terminal globular domain homologous to the immune complement C1q (dark grey). Circulating human CTRP3 exists in two isoforms encoded by alternatively spliced transcripts.

6.1. CTRP1

6.1.1. CTRP1- biomarker for early diagnosis of T2DM

CTRP1 is an adipokine predominantly produced by the stromal-vascular cells of adipose tissue, with insulin sensitizing effects and enhancements of fatty acid oxidation and energy expenditure [77]. Xin Y et al demonstrated that patients with type 2 diabetes exhibit significantly increased plasma CTRP1 levels compared to the healthy subjects. Moreover, the proportion of diabetic patients with high plasma CTRP1 levels was greater than the proportion with low plasma CTRP1 levels [78]. Pan X, et al. also approved that serum CTRP1 concentrations were significantly increased in subjects with T2D compared with the age- and gender-matched healthy subjects, moreover, they indicated that serum CTRP1 levels were strongly associated with insulin secretion and sensitivity in both T2D and healthy subjects [79]. The paradoxical increase of serum CTRP1 levels in T2DM subjects may be due to a compensatory response to the adverse glucose and lipid metabolism. Which suggest CTRP1 may be potential novel biomarkers for the prediction and early diagnosis of T2DM, even provide new ideas for the treatment of diabetes in the future. But this needs further investigation (Figs. 2 and 3).

6.1.2. CTRP1- evaluate cardiovascular risk

In addition, CTRP1 functions as a pivotal mediator linking lipid dysregulation to inflammatory response in macrophages [80]. Previous studies have reported that CTRP1 promotes the development of atherosclerosis by fostering production of inflammatory cytokines and leukocytes-endothelium interactions [81]. Interestingly, conflicting results have also been reported. D. Yuasa, et al. found that CTRP1 protects against myocardial ischemic injury in the heart via reducing apoptosis and inflammatory response. The seemingly conflict role of CTRP1 in different studies might be due to the differential role of CTRP1 in distinct cell types [82]. Yuasa D, et al who is the first group who investigated whether circulating level of an adipokine C1q/TNF-related protein (CTRP) 1 is associated with the prevalence of CAD. Then they demonstrated that increased levels of circulating CTRP1 are associated with the prevalence of CAD. Which is independent of conventional risk factors for CAD, Like: age, diastolic BP, glucose, total cholesterol, LDL-cholesterol. Therefore, CTRP1 may be a useful biomarker for evaluation of cardiovascular risk [83]. But whether CTRP1 gets involved in the pathogenesis of cardiovascular complications in T2DM is still unknow. Which needs deeper research.

6.2. CTRP3

6.2.1. CTRP3- biomarker of diabetic complications

CTRP3 (also known as CORS-26, cartducin and cartonectin) is a member of CTRP family [84]. There is evidence that CTRP3 level has a negative association with leptin levels. CTRP3 also reduced gluconeogenesis and subsequent glucose output in hepatocytes [85]. Interestingly, Studies on serum levels of CTRP3 in patients with diabetes are contradictory. A study by Choi et al. reported increase of CTRP3 levels in diabetes [86], but another study showed decrease in newly diagnosed T2D [87]. This conflicting results of CTRP3 in T2D can use the duration of T2D to explain. We suspect that long-term hyperglycemia and insulin resistance stimulate the release of CTRP3. Ahmed SF et al. indicated that the decreased levels of CTRP3 in female patients suffering from CAD secondary to long standing T2D when comparing to T2D alone. This novel finding highlights the possible use of CTRP3 as a diagnostic and prognostic marker in the development of CAD in female patients with long standing T2D [88]. Yan Z, et al revealed that CTRP3 deficiency was associated with proliferative diabetic retinopathy (PDR: a serious and widespread complication of diabetes), which demonstrated that circulating CTRP3 may serve a valuable role as a biomarker screening for diabetic retinopathy (DR), and may be an indicator of DR severity [88].

6.2.2. CTRP3- has cardio-protective properties

Different studies have reported that this adipokine has cardio-protective properties. It can be explained by the findings of Yi et al. they demonstrated that CTRP3 directly prevented apoptotic death of cardiomyocytes, increased cardiomyocyte survival/regeneration, attenuated postinfarct fibrosis, and enhanced cardiomyocyte expression of angiogenic cytokines inductive of robust angiogenesis, thus attenuating post-MI remodeling and augmenting post- MI contractile function [89]. Moreover, This protein was found to inhibit inflammation and improve insulin sensitivity in 3T3-L1 adipocytes [90]. One study reported a new function of CTRP3 as a regulator of angiogenic processes. CTRP3 promoted proliferation and migration of mouse endothelial MSS31 cells in a dose-dependent manner [91]. Furthermore, CTRP3 inhibits high glucose high lipid-induced VCAM-1 expression in an AMPK-dependent manner in human retinal microvascular endothelial cells(HRMECs), suggesting the novel therapeutic potential of CTRP3 for the treatment of DR [88]. Hasegawa N, et al. Indicated that after the program of 8-wk aerobic training in middle aged and older adults significantly elevated circulating CTRP3 level. Furthermore, negative correlations between circulating CTRP3 level and arterial stiffness. Therefore, the increase in serum CTRP3 level in response to aerobic exercise training may contribute to the reduction in arterial stiffness in middle-aged and older adults, and these adipokines are potential novel biomarkers of exercise induced decrease in arterial stiffness [92]. In conclusion, CTRP3 exerts protective effects on the cardiovascular system to reduce complications caused by long-term glycolipid metabolism disorder, suggesting that CTRP3 might be a novel therapeutic target.

6.3. C1q/TNF-related protein (CTRP) 9

6.3.1. CTRP9- A controversial adipokine in diabetic patients with CVD

CTRP9, a secreted glycoprotein discovered in 2009, has the highest similarity to adiponectin and is predominantly expressed by adipose tissue. Unlike adiponectin, CTRP9 is expressed at similar levels in adipocytes and stromal vascular fraction(SVF) [93] Ahmed SF et al associated the possible role of CTRP3, CTRP9 and MCP-1/CCL2 in the

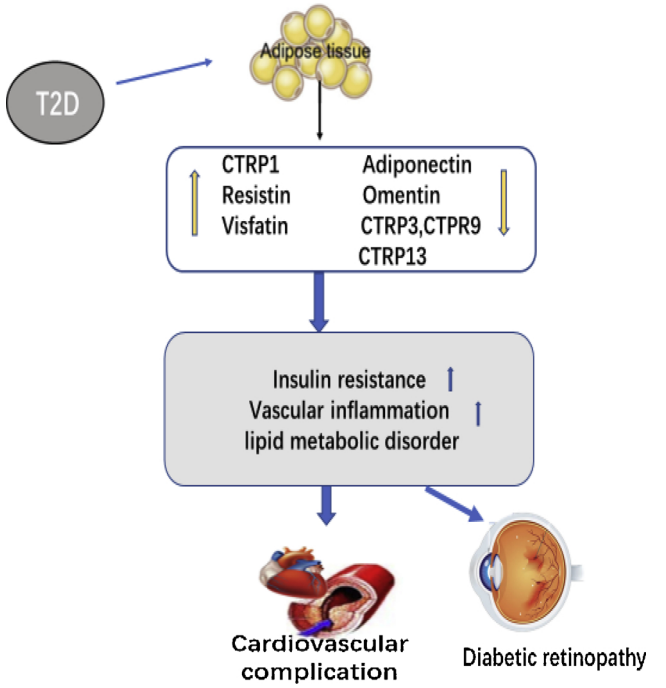

Fig. 2. (A) The balance between pro-inflammatory adipokines and protective adipokines in type 2 diabetes is disturbed, the change of adipokines level is more significant in type 2 diabetic patients who have high risk of developing cardiovascular diseases. These adipokines cause the occurrence of cardiovascular complications by promoting inflammation and directly acting on endothelial cells and myocardial cells. (B) CTRP3 deficiency was associated with proliferative diabetic retinopathy.

diagnosis and prognosis of CAD complication in T2D postmenopausal females, and find out that CTRP9 levels were significantly decreased in those patients with CAD secondary to T2D [94]. Conflicting results have been reported by Moradi N, et al. they indicated that the circulating CTRP9 levels were independently associated with increased risk of CAD and T2DM. The results revealed increased circulating levels of CTRP9 in T2DM and CAD individuals which suggests a compensatory response to insulin resistance, inflammatory milieu and endothelial dysfunction. These observed discrepancies may have resulted from differences such as duration of diabetes and ethnicities between studies. however, more studies are needed to confirm this [95]. The results of this study were in line with a study conducted by Asada et al, in which a positive association between serum CTRP9 levels and atherosclerosis in T2DM patients was demonstrated [96]. Asada found that increased serum CTRP9 levels in newly diagnosed T2DM patients [97], This study indicated the upregulation of CTRP9 likely reflects a compensatory response to hyperglycemia, hyperinsulinemia or insulin resistance, or a defensive response for surmounting metabolic stress or resistance to CTRP9 action, as is the case with insulin or leptin resistance [98].

6.3.2. CTRP9-the role of CTRP9 in peripheral blood vessels in T2D

Jung CH. et al indicated that serum CTRP9 concentration was significantly and positively associated with arterial stiffness in subjects with type 2 diabetes. Furthermore, this association was independent of conventional cardiovascular risk factors and serum levels of total adiponectin. this positive association between serum CTRP9 concentration and increased arterial stiffness might be a compensatory response to overcome the atherogenic milieu in type 2 diabetes [99]. However, Jiang W et al conducted a study which demonstrated that CTRP9 levels were negatively associated with the severity of peripheral arterial disease (PAD) in T2DM. This association was independent of adiponectin and conventional atherosclerotic risk factors. A low serum level of CTRP9 could provide supplemental information on diabetes patients to predict the possibility of the deterioration of PAD [100]. Besides, the role of CTRP9 plays in the establishment of microvascular damage also be discovered, Fujita T et al indicated that CTRP9 may reflect endothelial metabolic function besides of endothelial elastic function and reflects diabetic renal vascular risk in association with atherosclerosis and abnormal glycose metabolism besides an impaired vasorelaxant function in patients with T2DM [25]. According to the research provided above, we can make bold guesses CTRP9 could be a potential marker recommended for the clinical use in the diagnosis, prognosis and follow up of patients with T2D at risk of developing CVD. Extension to this current study using a larger sample size, comparing newly diagnosed T2D patients with long standing T2D patients, should be done to support the previous findings.

6.3.3. CTRP9-potential as therapeutic agents

CTRP9 can activate a variety of signaling pathways to regulate glucose and lipid metabolism, vascular relaxation and cell differentiation. Several beneficial effects of CTRP9 for the cardiovascular system have been reported. It has higher vasoactive potency than adiponectin [101], has a protective role in remodeling after acute myocardial infarction [102], decreases inflammation [103] and inhibits vascular smooth muscle cell proliferation [104–106] A similar result is also observed in mice with myocardial ischemia-reperfusion injury [107], and in subjects with coronary atherosclerosis disease (CAD). Moreover, serum CTRP9 levels are positively correlated with high-density lipoprotein cholesterol (HDL-C) levels in these CAD patients, suggesting that CTRP9 may be a potential biomarker of atherosclerosis [108] Consistently, overexpression of CTRP9 protects mice from diet induced obesity, a well-known risk factor for atherosclerosis [109], Injection of an adenoviral vector expressing CTRP9 via mouse jugular vein dramatically inhibits neointimal formation after left femoral arterial injury [110]. As above mentioned CTRP9 is known to protect against atherosclerosis and is reported to reduce myocardial infarct size and hypoxia-induced apoptosis of cardio-myocytes [111]. Taken together, these results indicate that replenishment of CTRP9 might be effective for attenuating vascular damages in diabetic states.

6.4. CTRP13- beneficial adipokine to diabetes

CTRP13 is another member of the CTRP family, which is mainly expressed in adipose tissue and can increase insulin-mediated glucose uptake and reduce gluconeogenesis [112].This protein has also a crucial role in regulating food intake and body weight [113]. Afrookhteh A, et al. indicated that CTRP13 is a novel adipokine associated with T2D in humans as its serum level was significantly lower in T2D patients and also was inversely correlated with insulin resistance and fasting blood sugar in humans [114]. which consistent with Fadaei R, et al. who reported decreased serum levels of CTRP13 in the CAD, T2DM and CAD + T2DM patients and group CAD + T2D is the lowest. Moreover, CTRP13 has a significant negative correlation with elevated TG, TC and LDL-C and a positive correlation with HDL-C. Since reduced levels of HDL-C is an important aspect of dyslipidemia in T2DM as well as a classical and important risk factor for CAD [115].

The regulatory effects of CTRP13 in lipid metabolism and the cardiovascular system is beneficial. It can be improved by Wang C, et al, who indicated that CTRP13 inhibits atherosclerosis via autophagy-lysosome-dependent degradation of CD36. In this study, they collected blood samples from patients of coronary artery diseases and apolipoprotein E (ApoE)-/- mice that were fed a Western diet for 12 weeks to induce atherosclerosis and found that ectopic CTRP13 infusion in vivo dramatically decreased lesion areas, as well as reduced inflammatory responses with less macrophage content. In primary peritoneal macrophages in vitro, CTRP13 supplement reduced oxidized LDL uptake, foam-cell formation, and trapping [116]. CTRP13 supplementation may be a promising therapeutic avenue for atherosclerosis. But so far it has not been studied in the conditions of T2DM and CAD. However, it is still

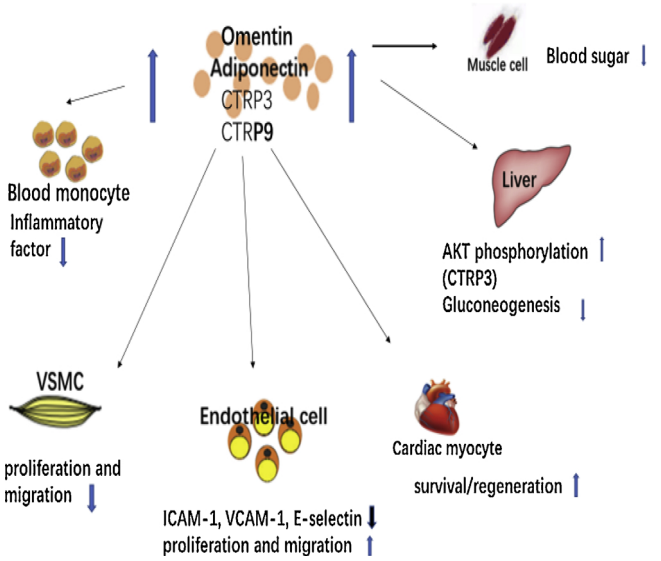

Fig. 3. (A) Effect of adipokines on glucose metabolism: CTRP3 exerts antidiabetic effects in the liver by inducing AKT phosphorylation and by reducing gluconeogenesis; CTRP9 activates AMPK, Akt and p42/44 MAPK in C2C12 myotubes, and stimulation of muscle glucose uptake might contribute to reduced blood glucose; CTRP13 exerts antidiabetic effects and improves insulin sensitivity by inhibiting gluconeogenesis in the liver. (B) Adipokines such as adiponectin, omentin, CTRP3, CTRP9, CTRP13 exert beneficial effects on cardiovascular diseases by directly acting on the component cells in the heart and blood vessel.

unclear whether CTRP13 has anti-atherosclerosis effect in diabetic patients too, which needs deeper studies.

7. Conclusion

Adipose tissue functions as a key endocrine organ by releasing multiple bioactive substances, known as adipokines, that have pro-inflammatory or anti-inflammatory activities. Imbalanced production of adipokines in diabetic patients can contribute to the development of metabolic and cardiovascular complications. In this review, we discussed that adiponectin, omentin, CTRP3, CTRP9 and CTRP13 are downregulated in diabetic patients, these adipokines with cardiovascular protective properties, could represent therapeutic molecules targeted for preventing or treating cardiovascular diseases in type 2 diabetic patients. On the contrary, resistin, visfatin and CTRP1 are upregulated in type 2 diabetes and promote the vascular dysfunction, these adipokines can be biomarkers of cardiovascular complications in diabetic patients. Further research should focus on: (i). How to determine a critical concentration as a noninvasive method to assess the risk of future cardiovascular events in the diabetic population. (ii) How to maintain the beneficial effects and reduce adverse effects of adipokines as a new strategy for the treatment of cardiovascular complications of diabetes.

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Authors' contributions

These authors contributed equally to this work in literature search and writing

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