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Emerging roles of C1Q tumor necrosis factor-related proteins in metabolic diseases

Manjunath Ramanjaneya[*†], Jayakumar Jerobin[†], Ilham Bettahi, Kodappully Sivaraman Siveen and Abdul-Badi Abou-Samra[*]

Abstract

Obesity and insulin resistance are key elements of the metabolic syndrome, which includes type 2 diabetes (T2D), dyslipidemia, systemic inflammation, hypertension, elevated risk for cardiovascular diseases, non-alcoholic fatty liver disease (NAFLD) and polycystic ovary syndrome (PCOS). C1Q Tumor necrosis factor-related proteins (CTRPs) have recently emerged as important regulators of metabolism as a core component in the interrelationship between insulin resistance, adiposity and inflammation. To date 15 CTRP members have been identified and most of the CTRPs are dysregulated in obesity, T2D, coronary artery disease and NAFLD. Pharmacological intervention and lifestyle modification alter expression of CTRPs in circulation and in metabolically active tissues. CTRPs enhance metabolism mainly through activation of AMPK/AKT dependent pathways and possess insulin sensitizing properties. Thus dysregulated expression of CTRPs in metabolic disorders could contribute to the pathogenesis of the disease. For these reasons CTRPs appear to be promising targets for early detection, prevention and treatment of metabolic disorders. This review article aims at exploring the role of CTRPs in metabolic syndrome.

Keywords: Obesity, Type 2 diabetes (T2D), Metabolic syndrome (MS), Polycystic ovarian syndrome (PCOS), Non-alcoholic fatty liver disease (NAFLD), Adipose tissue and C1Q tumor necrosis factor-related proteins (CTRPs)

Introduction

Adipose tissue is a dynamic endocrine organ that stores excess of energy in the form of triglycerides and secretes bioactive molecules termed as adipokines/adipocytokines that, amongst other key functions, contribute to glucose homeostasis and fatty acid metabolism [1–4]. C1q protein family contains over thirty secreted multimeric proteins that share a C-terminal domain homologous to the globular domain of the immune complement C1q [5, 6]. This family also include the C1Q Tumor Necrosis Factor-Related Proteins (CTRPs) that are also implicated in the regulation of lipid and glucose metabolism [7].

Adiponectin, a key adipokine is a multivariate protein found in abundance in healthy individuals as an insulin sensitizer and its deficiency may play a role in the pathogenesis of the metabolic syndrome (MS) [8]. CTRPs are a group of fifteen proteins with a role similar to that of adiponectin in metabolism (Table 1) [7]. CTRPs contain four distinct domains, which include a short variable domain, a C-terminal C1q globular domain, a collagenous domain and an N-terminal signal peptide (Fig. 1) [7].

CTRPs are widely expressed in central and peripheral tissues such as adipose tissue, liver, skeletal muscle, and heart in both rodents and human. CTRPs have been implicated in the regulation of insulin sensitivity and fatty acid oxidation in major metabolic organs such as liver, heart, skeletal muscle and adipose tissue (Fig. 2) [38]. Dysfunction of CTRPs are associated with metabolic abnormalities such as obesity, insulin resistance (IR), type

* Correspondence: mramanjaneya@hamad.qa; ASamra@hamad.qa
[†]Manjunath Ramanjaneya and Jayakumar Jerobin are joint first authors.
Qatar Metabolic Institute and Translational Research Institute, Academic Health System, and Department of Medicine, Hamad Medical Corporation, PO Box 3050, Doha, Qatar

Table 1 Summary of CTRPs expression in pathophysiological states and their metabolic functions

| CTRP	Tissue expression	Obesity	Diabetes	CVD	NAFLD	PCOS	Signaling pathways& Physiological function	References
CTRP1	Adipose tissue, heart, liver, muscle, ovary, kidney, placenta, prostate	↑ human ↑ ob/ob mice	↑ T2D	↑ CAD ↑ MI	↑ NAFLD ↑ NAFLD with T2DM	–	AMPK, p44/42-MAPK ↑ FA oxidation, ↑ Glucose uptake, CTRP1 loss disrupts lipid and glucose homeostasis, CTRP1 KO mice prone for MI Rosiglitazone ↑ CTRP1	[9–22]
CTRP2	Adipose tissue, lung, liver, testis, uterus, Stromal vascular cells	↑ ob/ob mice	–	↑ CAD	–	–	AMPK, ACC, p44/42-MAPK ↑ Energy expenditure; ↑ Insulin sensitivity; ↑ Lipid tolerance; ↑ Glycogen accumulation and FA oxidation in myotubes,	[7, 10, 19, 23–26]
CTRP3	Adipocytes, Fibroblast, pancreas, kidney, thymus,	↓ Human ↓ DIO ↑ ob/ob mice	↓T2D	↓MI	↓ PCOS women	↓ PCOS women	p-ERK, p-p38 MAPK, p-AKT, AMPK ↓ Adipogenesis, ↓ Gluconeogenesis, CTRP3 KO reduces liver size, ↑CTRP3 with fasting GLP-1R agonist improves IS by increasing CTRP3	[27–37]
CTRP4	Brain, Adipose tissue, Skeletal muscle	↑ ob/ob mice	–	–	–	–	↓Apetite ↓ Body weight.	[7, 38, 39]
CTRP5	Adipose tissue, liver, Heart, Brain, Lung, Pancreas, uterus, thymus, skeletal muscle	↑ Human ↑ ob/ob mice	↓ T2D	↓ CAD	↓ NAFLD ↓ NAFLD + T2DM	–	AMPK, ACC, p38 MAPK ↑ Insulin action and hepatic steatosis due to loss of CTRP5 Regulates glucose and lipid metabolism ↓Insulin sensitivity in liver	[10, 26, 40–44]
CTRP6	Adipose tissue, heart	↑ob/ob mice ↑ Human					AMPK, Akt ↑ FA oxidation Regulate glucose and lipid metabolism. ↓ MI induced Cardiac fibrosis.	[26, 45, 46]
CTRP7	Skeletal muscle, adipose tissue, lung, placenta	↑Human ↑ob/ob mice		↑ CAD			Calorie restriction ↑CTRP7 impairs glucose metabolism	[25, 26, 47–49]
CTRP9	Adipose tissue, Brain, heart, liver	↑Human ↓ DIO mice	↑ T2D	↓ MI ↓ CAD		↑ PCOS women	P44/42 MAPK, Akt, AMPK/ eNOS/NO ↑ FA oxidation ↓ Apetite ↓ Ischemic reperfusion injury ↓ Hepatic and skeletal muscle triglycerides protect against hepatic steatosis and insulin resistance	[34, 50–58]
CTRP10	Adipose tissue, Brain, Placenta	↑ ob/ob mice	–		–	–	–	[26, 38]
CTRP11	Adipose tissue, Brain, Kidney						P44/42 MAPK ↓ Adipogenesis	[7, 38, 59]
CTRP12	Adipose tissue.	↓ ob/ob ↓ DIO	↓T2D			↓ PCOS women	PI3K/Akt, AMPK Antiinflammatory ↑ Insulin sensitivity ↓ Gluconeogenesis Rosiglitazone ↑ CTRP12	[14, 60–62]
CTRP13	Brain, adipose tissue						↓ Food intake ↑ Insulin sensitivity Rosiglitazone ↑ CTRP13	[63, 64]
CTRP15	Skeletal muscle, adipose tissue, liver	↓HFD mice		↑CAD			PI3/Akt/ mTOR ↑ Fatty acid uptake in adipocytes, hepatocytes and skeletal muscle	[7, 38, 49, 65, 66]
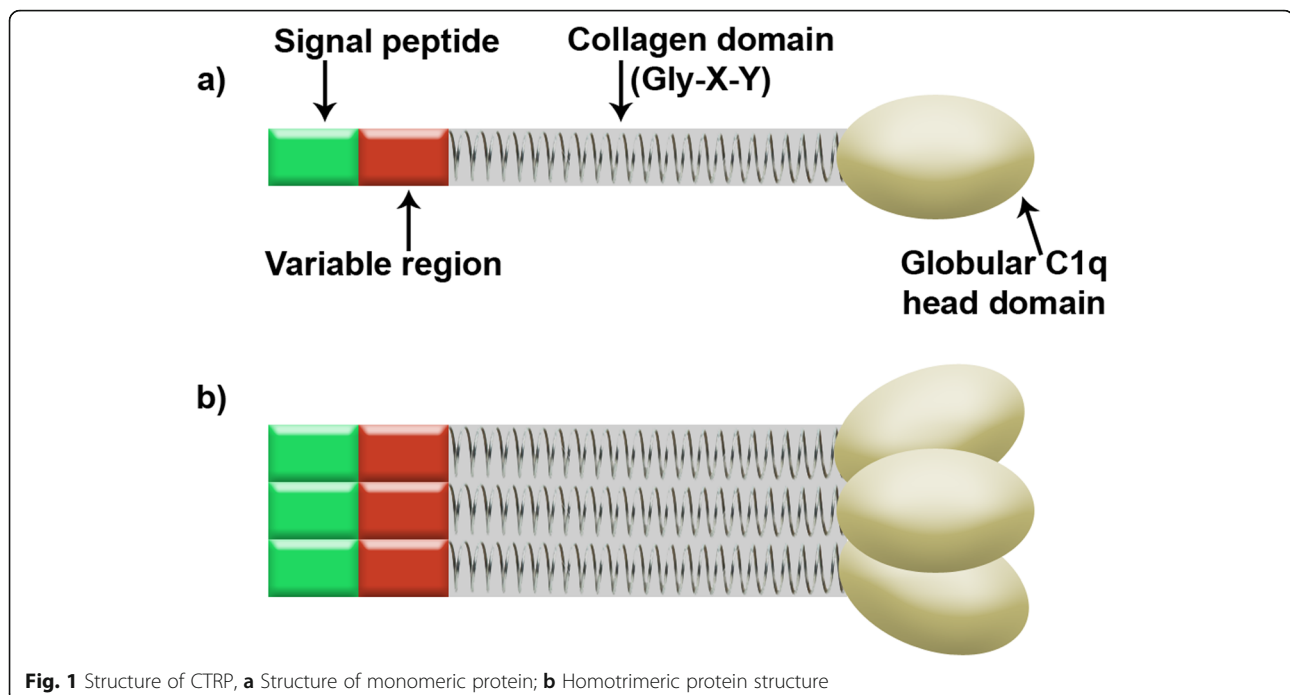
Fig. 1 Structure of CTRP, **a** Structure of monomeric protein; **b** Homotrimeric protein structure

2 diabetes (T2D), cardiovascular disease (CVD), non-alcoholic fatty liver disease (NAFLD) and PCOS [67–70]. Recently studies are focused on the potential role of CTRPs on metabolic abnormalities [7]. This review aims at exploring the potential role and importance of CTRPs in metabolic abnormalities.

Appetite regulation by CTRPs

The metabolic consequences of the obesity arise from imbalance between energy intake and energy expenditure as a result of complex and poorly understood interactions between genes and environmental factors that can be influenced by behavior. In some individuals excess energy intake leads to excessive fat accumulation in the abdominal region, visceral adiposity, with deleterious effects on health [71, 72]. Obesity rates continue to rise globally despite efforts from public campaign and personal efforts. This occurs due to abundant access to energy dense food, failure of homeostatic mechanisms to regulate appetite and metabolic adaptations to prevent further weight gain [73]. Efforts to curb food intake and increase physical activity are largely ineffective. Calorie restriction increases lifespan of rodents and unicellular organisms, the effect on humans remains uncertain despite the fact that surrogate markers of metabolic health improve dramatically [74, 75].

CTRP1 transgenic mice are obesity resistant; they gain less body weight on a high fat diet (HFD) compared to controls [9]. Over expression of CTRP1 enhances energy expenditure, fatty acid oxidation and reduced fat mass [9]. However, CTRP2 transgenic mice have no role in appetite regulation and are not protected from obesity when challenged with HFD. These transgenic mice have improved insulin tolerance and a greater capacity to handle acute lipid challenge relative to littermate controls. Deletion of CTRP2 leads to secretion of hepatic triglyceride and adipose tissue lipolysis [23, 24]. Similarly, CTRP3 transgenic mice also show no differences in appetite, glucose metabolism or body weight compared to the wild type, but are resistant to the onset of hepatic steatosis, have lower serum TNF-alpha levels, and demonstrate a mild improvement in systemic insulin sensitivity [27]. Caloric restriction enhances insulin sensitivity in young and senescent rats. Whereas adiponectin levels are increased only in young rats; the senescent animals show increased expression of CTRP2 and CTRP7 in skeletal muscles; however, this did not increase AMPK activation [25]. Thus, the improvement in insulin sensitivity by caloric restriction in the old animals is not due to adiponectin induction [25] this effect may be induced by some unidentified proteins. This could be one possible reason for the dampened insulin sensitivity associated with aging.

Other CTRP family members such as CTRP4, CTRP9 and CTRP13 are highly expressed in the hypothalamus and may regulate appetite and body weight (Fig. 2), [7, 50]. CTRP4 expression in the mouse hypothalamus is increased by refeeding after overnight dietary restriction [39]. Central administration of recombinant CTRP4 inhibits appetite and lowers body weight in HFD fed mice with decreased expression of neuropeptide-Y (NPY) and the agouti-related protein (Agrp) [39]. Deletion of CTRP
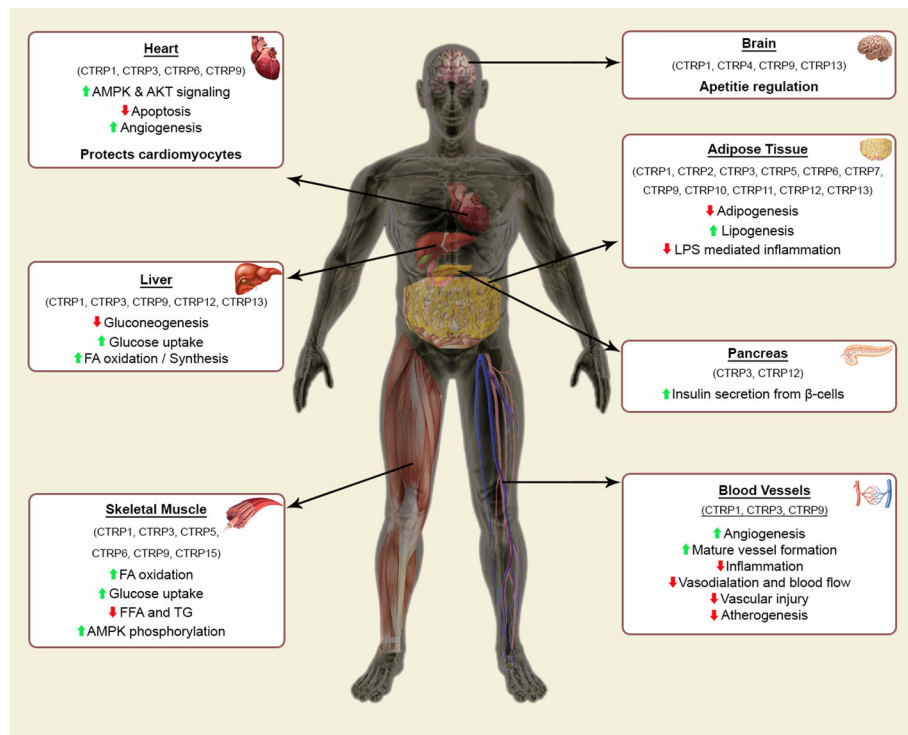
Fig. 2 Expression and functional role of CTRPs in major metabolic tissues and organs

9 in mice increased food intake, decreased insulin sensitivity and promoted hepatic steatosis [76]. In contrast CTRP9 transgenic mice were lean and resisted weight gain induced by a high-fat diet, mainly through reduced food intake and improved basal metabolism [76]. Taken together the data indicate that both CTRP4 and CTRP9 may be important regulators of appetite and food intake in the mouse.

The situation is complicated further by the observation that obese mice show increased hypothalamic CTRP13 expression that can be downregulated by calorie restriction and upregulated by high fat diet [63]. Intracerebroventricular (ICV) administration of recombinant CTRP13 in mice inhibits food intake and promotes weight reduction. This was accompanied with increased respiratory exchange ratio; this suggest increased free fatty acid (FFA) release from adipocytes may act as substrates for fatty acid oxidation in the skeletal muscle and liver. ICV administration of the orexigenic neuropeptide AgRP promoted CTRP13 expression. On the contrary administration of CTRP13 inhibited AgRP expression centrally. Calorie restriction inhibits hypothalamic Ctrp13 expression and increases the expression of NPY and Agrp [39, 63]. In contrast, when calorie restriction coupled with enhanced physical activity, both CTRP13 and Agrp were upregulated in the hypothalamus. This suggests that AgRP and CTRP13 regulate each other expression and form a local hypothamic feedback loop that regulates appetite [63].

CTRPs in skeletal muscle metabolism

The skeletal muscle plays an important role in fatty acid and glucose metabolism [77, 78]. Stimulation of skeletal muscle with insulin increases glucose uptake and glucose utilization; excess glucose is converted to stored energy in the form of glycogen [79]. IR in skeletal muscles is an important mechanism in T2D [80]. Several growth factors and myokines secreted from muscles modulate the metabolic and inflammatory processes [80, 81]. CTRP1 transgenic mice have increased fatty acid oxidation and energy expenditure in muscle cells through AMPK activation of acetyl co-enzyme A carboxylase (ACC) dependent pathway [9]. In muscle cells, CTRP5 and CTRP6 regulate glucose and lipid metabolism by promoting GLUT4 translocation and fatty acid oxidation through activation of AMPK [40, 41, 45] (Fig. 3).

In murine C2C12 myocytes, CTRP9 activates p44/42 MAPK, Akt and AMPK signaling pathways, which are important mediators of insulin signaling [51]. Mice over-expressing CTRP9 had lower hepatic and skeletal muscle triglyceride levels, enhanced basal metabolic rate, suppressed food intake, increased body energy expenditure and were protected against diet induced obesity (DIO), IR and hepatic steatosis [76]. In adipose tissue, hepatocytes and skeletal muscle stimulation with CTRP15 enhanced fatty acid uptake without altering adipose tissue lipolysis [65, 82].
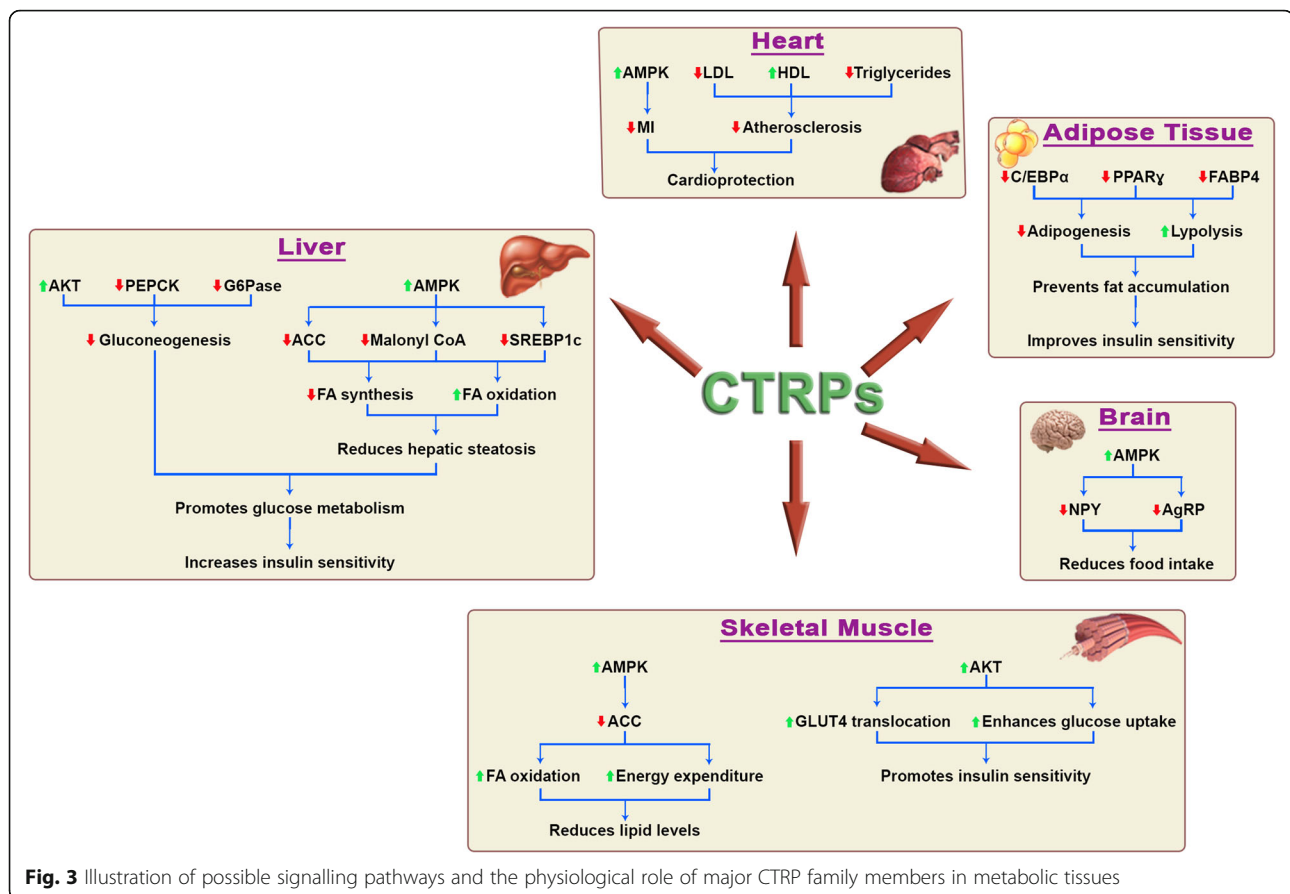
Fig. 3 Illustration of possible signalling pathways and the physiological role of major CTRP family members in metabolic tissues

CTRPs in obesity and T2D

Obesity accompanied by IR is a key factor in the development of T2D and MS [83]. Current thinking is that adipose tissue secretes adipokine that regulate central and peripheral metabolic pathways thereby modulating homeostasis, blood pressure, lipid and glucose metabolism [42, 47, 84]. Most CTRPs are highly expressed in adipose tissues and have been implicated in the pathogenesis of obesity and T2D [38]. CTRP1, 2, 3, 4, 6 and 7 are also abundantly expressed in leptin-deficient ob/ob mice suggesting that leptin might regulate the expression of these family members (Table 1) [7, 26, 39]. In obese and T2D subjects circulating adiponectin levels are decreased. The adiponectin levels positively correlate with markers of insulin sensitivity and may protect against the MS [85–87]. Similar to adiponectin, CTRPs protects against obesity and T2D through enhancing insulin sensitivity and metabolism [10, 23, 76]. This explains why the members of the CTRP family are downregulated in tissues such as skeletal muscle, adipose tissue and liver in HFD-fed mice and also the circulatory levels are lower in obese and T2D compared to controls [26].

Circulating CTRP1 is higher in prediabetes, preeclampsia, T2D patients and positively correlates with fasting glucose, body mass index (BMI), glycated hemoglobin (HbA1C), low density lipoprotein (LDL), fibroblast growth factor (FGF21), Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) and negatively correlate with adiponectin [11–14, 88, 89]. This is in contrast to diet induced obese (DIO) mice that have significant reductions in circulating CTRP1 levels [9]. Unlike CTRP1, CTRP2 levels in the circulation are not significantly different in obese and control mice [23], whereas the circulating CTRP3 are lower in T2D and negatively correlates with IR. Elevated levels of CTRP3 were observed in women with gestational diabetes mellitus [28–30, 90–92]. CTRP3 levels are lower in DIO rodents than in control animals and the level increases after administration of a glucagon like peptide-1 (GLP-1) agonist [31]. CTRP3 is increased during fasting, inversely correlated with leptin and its levels are higher in leptin-deficient ob/ob mice [32]. CTRP3 added to human hepatocytes in vitro suppresses the gluconeogenic pathway thus showing a direct effect on gluconeogenesis [32]. Stimulation of pre-adipocytes with CTRP3 decreases adipogenic markers C/EBPα, PPARγ, FABP4 thereby inhibits adipogenesis and negatively regulates lipid metabolism [93].

Circulatory CTRP5 levels is abundantly expressed in murine adipose tissue and liver. CTRP5 KO mice have

lower fasting insulin levels and when challenged with high fat diet these mice are more tolerant to lipid accumulation and are less prone for hepatic steatosis and have enhanced insulin action [42]. From this study it appears that CTRP5 may act as a negative regulator of glucose metabolism and promote IR. Further circulating CTRP5 shows sexual dimorphism, with higher levels found in female than male mice [26, 40]. CTRP6 was elevated in adipose tissue of obese T2D patients and this positively correlated with BMI [94]. CTRP7 is significantly elevated in obese subjects and positively correlates with marker of IR such as BMI, glucose, insulin and HOMA-IR [48]. CTRP7 deficient mice are protected from obesity and fatty liver [47] and its circulating levels are increased in the ob/ob mouse [26].

A significant reduction in circulating CTRP9 levels was observed in obese preeclampsia whereas in obese and T2D subjects it was found to be elevated [52–54, 95]. The circulating CTRP9 levels decreases with calorie restriction and increase upon re-feeding [76]. However, for CTRP11, both fasting and re-feeding have no effect on adipose tissue CTRP11 expression in DIO and ob/ob mice [59]. The circulatory and adipose tissue expression of CTRP12 were found to be lower in both DIO and leptin-deficient ob/ob mice [60, 61]. CTRP13 is expressed at relatively low levels in adipocytes compared to adiponectin, the most abundantly expressed adipokine [64]. Lean female mice have higher CTRP13 transcripts in adipose stromal vascular fraction compared to male. However, in obesity the expression pattern switches, obese male mice have higher circulating CTRP13 compared to lean and no significant difference were observed between lean and obese female mice suggesting a potential role in energy metabolism [63, 64]. Circulatory CTRP15 levels are lower in obese mice [65]. Food deprivation, exercise and gender influence circulatory levels of CTRP15. Furthermore, calorie restricted female mice had higher circulating CTRP15 compared to the males [65]. This suggests that circulating CTRPs might serve as novel biomarkers for the early detection and intervention for obesity-linked T2D [7, 96].

Pharmacological intervention of CTRPs in obesity and diabetes

The peripheral administration of CTRPs in obese and diabetic mice results in lower circulatory glucose levels and promotes insulin sensitivity (Table 1) [23, 32, 51, 76]. The administration of CTRP1 resulted in time dependent reduction of blood glucose levels [26]. Administration of recombinant CTRP3 to leptin deficient ob/ob mice lowers the blood glucose levels without altering glucagon, insulin and adiponectin levels in both wild type and ob/ob mice [32]. CTRP6 gene deletion

increased the metabolic rate, improved action of insulin and energy expenditure in DIO mice [94]. The CTRP9 transgenic mice were lean, had lower insulin levels and maintained glucose load better compared to control littermates [76]. Recombinant CTRP9 administration improves the fatty oxidation by activating the AMPK pathway [50]. The administration of CTRP12 in mice decreased resistin levels but had no effect on other adipokines such as leptin, adiponectin and plasminogen activator inhibitor-1. Furthermore, CTRP12 suppressed gluconeogenesis and promotes glucose uptake by activating the PI3 kinase/Akt pathway [60]. The administration of myonectin (CTRP15) to obese mice has no effect on blood glucose and serum triacylglycerol levels [7, 65, 82]. This may be due to the shorter half-life leading to rapid degradation of CTRP15 in the circulation.

Insulin and metformin treatment does not alter the circulatory CTRP1 levels in T2D patients [12]. Administration of the GLP-1 receptor agonist exendin improves insulin sensitivity in IR and T2D rats by increasing CTRP3 levels in circulation and in the adipose tissue [31]. Furthermore, rosiglitazone treatment up-regulates circulating CTRP1 levels in diabetic subjects and also increases expression of CTRP12 and CTRP13 in adipose tissue explants thus providing the evidence for PPARγ mediated regulation of CTRPs [9, 64, 97].

CTRPs and cardiac function

Obesity is a major risk factor for CVD mortality [98]. Obesity linked complications such as glucose intolerance are associated with cardiac injury and prognosis of myocardial infarction (MI) [99, 100]. Distorted circulating CTRPs are linked to obesity and IR that are associated with the prevalence and progress of the CVD [12, 15, 16, 101]. In patients with coronary artery disease (CAD) and atherosclerosis, circulating CTRP1, CTRP2 and CTRP3 were elevated and increased further with severity of CAD [17–19, 88]. Patients with acute myocardial infarction had much higher CTRP1 compared to patients with stable/unstable angina. CTRP1 levels were further increased with severity of vessel disease. Patients having triple-vessel disease had significantly higher CTRP1 compared to subjects having single-vessel disease [17]. Moreover, CTRP1 in circulation positively correlate with the systolic blood pressure and triglycerides [16, 20]. Thus suggesting that elevated CTRP1 levels could be used as a potential biomarker for CAD and atherosclerosis in men [16, 20, 21].

Circulatory CTRP3 levels were lower in patients with both stable angina pectoris acute coronary syndrome and acute myocardial infarction [33]. Similarly, CTRP5 is a proatherogenic cytokine promoting oxidation of LDL and transcytosis in endothelial cells by upregulating a key molecule 12/15 lipooxygenase which mediates oxidation and

LDL trafficking via STAT6 signaling [102]. Circulating CTRP5 levels is lower in patients with IR and CAD [43]. Another member of CTRP family CTRP6 is also highly expressed in adult rat cardiomyocytes, and the levels are significantly reduced in infarct tissue following MI in rats [46]. CTRP7 was found to be higher in CAD patients compared to non-CAD subjects. The CTRP7 levels was highest in patients with triple vessel lesion compared to single vessel lesion CAD patients [49].

The closest adiponectin paralog CTRP9 is expressed about 100-fold higher in mice cardiac tissue compared to adiponectin [55]. In individuals with acute MI and coronary atherosclerosis, the CTRP9 expression in adipocytes and in circulation was lower [103]. Similarly, in rodents, CTRP9 levels decreased significantly in adipose tissues following myocardial ischemic reperfusion [55, 56]. In patients with T2D and those coexisting with CAD along with T2D had lower circulating CTRP9 levels associated with the prevalence of the CAD [34]. This report is intriguing given study from *Jia* et al., reported CTRP9 levels to be elevated in T2D [53].There are controversial finding on CTRP15 and CAD. *Nahrkhalaji* et al., found elevated CTRP15 levels in CAD patients and elevated CTRP15 levels were associated with insulin resistance, BMI and disease severity [49, 66]. However recent findings from *Zhang* et al., showed lower level of CTRP15 in triple vessel lesion patients compared to single vessel lesion patients and non-CAD patients [49]. Further studies on large cohorts are required to elucidate the role of CTRP15 in CAD.

Pharmacological intervention of CTRPs in cardiac disease

The peripheral administration of CTRP1 prevents platelet adhesion, aggregation and thrombosis induced by collagen in rodents and in primates [22]. In contrast another study eluded that CTRP1 administration in mice promotes atherogenesis [20]. Further studies are needed to understand better to therapeutically exploit CTRP1 as potential antithrombotic agents in clinical settings.

The mice pre-treated with recombinant CTRP3 prior to induction of MI had improved post-MI survival rate, restored cardiac function, lesser cardiomyocyte apoptosis and improved revascularization compared to control mice subjected to MI [35]. In addition CTRP3 also enhanced AKT phosphorylation and increased the expression of vascular endothelial growth factor, and hypoxia inducing factor-1α genes that are key mediators required for promoting angiogenesis and mature vessel formation. These effects were mediated independent of nitric oxide production [35]. These observations have clinical relevance in patients with MI; CTRP3 may be useful in the future as an adjuvant to other drugs aimed to restore cardiac function after myocardial ischemia and MI [35].

The transforming growth factor-beta1 (TGF-β1) induces the expression of CTRP3 in vascular smooth muscles (VSMCs) following blood vessel injury and further promotes proliferation of VSMCs [36]. The recombinant CTRP3 administration enhances angiogenesis in rodents through activation ERK1/2 and p38 MAPK signaling dependent pathways (Table 1) [104].

The knockdown of CTRP6 promotes TGF-β1-induced expression of cardiac fibrosis and over expression inhibits TGF-β1 suggesting TGF-β1 may be critically important for regulation of CTRP6 [46]. Furthermore, over expression of CTRP6 in rats through adenoviral- mediated delivery promotes activation of AMPK and AKT-dependent pathways, reduces cardiac hypertrophy, alleviated cardiac fibrosis, hampered myofibroblast differentiation and improves cardiac function post-MI [46]. CTRP9 knockout mice subjected to myocardial ischemia/reperfusion (MI/R) had severe tissue injury and increased cell death compared to controls. This was reversed by either overexpression or through the administration of recombinant CTRP9 which reduced gp91phox expression attenuated superoxide production and oxidative stress [105]. Furthermore in high fat diet fed mice subjected to MI/R, CTRP9 administration also improved cardiac function [105]. This report was further supported by findings where administration of CTRP9 reduces the hypoxia of MI/R through activation of AMPK pathway; thus, protecting the heart from cardiac ischemic injury and decreasing infarct size in response to the ischemic reperfusion [106].

Furthermore, in the apolipoprotein-E KO mice which are susceptible to develop atherosclerosis, administration of CTRP9 stabilized carotid plaques, probably via reduction in the secretion of macrophage proinflammatory cytokines (TNFα and MCP-1) [107]. CTRP9 might also be associated with the regulation of arterial stiffness in humans [108], as it was shown to promote vasorelaxation in human vascular endothelial cells and aortic rings via activation of the AMPK/eNOS/NO-dependent pathway (Table 1) [109]. It also prevents VSMCs proliferation via cAMP-dependent mechanism following arterial injury [110]. Interestingly treatment of a mouse model of acute myocardial infarction with CTRP9 ameliorates cardiomyocyte apoptosis, improves cardiac function and survival through activation of AMPK, PKA and AKT-dependent pathways (Fig. 2) (Table 1) [55]. Taken together these findings suggest that CTRPs might be useful biomarker for the diagnosis and treatment of CVD [7, 111].

CTRPs and non-alcoholic fatty liver disease

NAFLD is linked to IR, obesity and metabolic syndrome [112]. The IR in obese individuals leads to de novo synthesis of lipid and its accumulation in the liver [113, 114]. Disrupted levels of adipokines such as adiponectin,

visfatin, TNFα and IL-6 have been found in NAFLD patients, some of which play a key role in the pathophysiology of NAFLD [115, 116]. Therefore, circulating adipokines are currently being used as a surrogate biomarker to determine the prognosis of the disease [117]. Unlike adiponectin, which is lower in NAFLD patients [116], circulating CTRP1 levels were higher in patients with NAFLD and also in patients who had both T2D with NAFLD (Table 1) [15]. CTRP1 levels in these patients positively correlated with fasting blood glucose, BMI, HOMA-IR, γ-glutamyl transpeptidase, alanine transaminase and liver stiffness [15].

CTRP3 plays an important role in regulation of hepatic glucose production. CTRP3 transgenic mice are resistant to hepatic steatosis when fed on HFD and hepatic glucose-6 phosphatase expression was significantly reduced. However, no change was observed in the expression of PPARγ, *Cpt1a*, *Acox*s, *Acad*s and AMPK pathway between wild type and CTRP3 transgenic mice [27]. Administration of CTRP3 reduced blood glucose without altering glucagon, insulin and adiponectin levels in wild type, DIO and ob/ob mice. In hepatoma cells, CTRP3 stimulation reduced lipid accumulation and fatty acid synthesis by suppressing triglyceride synthesis genes (*Agpat*, *Gpat*, and *Dgat*) expression. In hepatocytes, CTRP3 suppressed gluconeogenesis by activating Akt pathway and decreasing the gluconeogenesis enzymes PEPCK and G6Pase independent of insulin (Fig. 3) [27, 32]. Circulatory levels of CTRP5 can be an independent risk factor for determining IR states such as T2D and NAFLD. In small group of human subjects circulating levels of CTRP5 were significantly reduced in T2D, NAFLD and patients with both T2D and NAFLD. From this study lower circulating CTRP5 appears to be an independent risk factor for IR states such as NAFLD, T2D and NAFLD with T2D in human subjects [44].

Genetic deletion of CTRP9 makes mice more prone to develop hepatic steatosis, these CTRP9 KO mice have higher appetite, increased lipid accumulation in the liver, decreased AKT phosphorylation, impaired hepatic insulin signaling and IR [50]. Expression of lipogenic genes *Srebp-1c and* acetyl-CoA carboxylase were higher in CTRP9 KO mice thus promoting lipid accumulation in the liver. However the fatty acid synthase and fatty acid oxidation regulatory genes (*Lcad* and *Mcad*) were unaltered. The administration of recombinant CTRP9 to these KO mice reduced hepatic lipid levels supporting the hypothesis CTRP9 can be important therapeutic target for NAFLD [50].

CTRP9 transgenic mice have lower hepatic and skeletal muscle triglyceride levels, these mice have improved metabolic profile and are protected from metabolic syndrome phenotypes such as IR, high fat diet-induced obesity and hepatic steatosis [50, 76]. Furthermore adenovirus-mediated CTRP9 overexpression in HFD-fed mice leads to suppression of ER stress markers, fatty acid metabolic genes SREBP-1c, lipid accumulation via activation of AMPK dependent pathway [57].

CTRPs and polycystic ovary syndrome
Polycystic Ovary Syndrome (PCOS) is one of the common hormonal disorders in women of reproductive stage [118]. It is a chronic pro-inflammatory state, commonly associated with menstrual dysfunction, diabetes-like phenotype, dyslipidemia, cardiovascular complications, obesity and metabolic syndrome [119]. Obese women are more likely to develop PCOS due to the accumulation of fat, which leads to the development of hyperinsulinemia and IR [120]. The circulating level of adiponectin has been suggested to be possible biomarker in PCOS individuals [121]. CTRP family members are differentially expressed in PCOS subjects. Circulating CTRP9 levels were similar in PCOS and control subjects and positively correlate with serum total cholesterol and LDL-C, the unfavorable lipids [58]. CTRP3 and CTRP12 might have a similar function in PCOS women since CTRP3 expression in adipose tissue and in circulation were lower in women with PCOS and augmented following metformin treatment [37]. In addition glucose stimulation reduced circulating CTRP12 levels while metformin treatment increased the CTRP12 expression in adipose tissue explants, at least in part through activation of AMPK dependent pathway [62].

Conclusion
The metabolic syndrome is a major global health problem associated with T2D, NAFLD and CVD. During the last decade many members of CTRPs were identified in many metabolic tissues and the CTRP family seems to be rapidly expanding. The CTRPs have diverse physiological functions regulates food intake, protects against hepatic steotosis, improves IR and protect against ischemic reperfusion injury and MI in rodents. However, the limitations are controversial findings from different studies showing opposite effects on circulating levels in certain pathophysiological conditions. The lack of clinical studies to translate findings from animals to human. Furthermore, in relationship to CTRP receptor identification it has been suggested CTRPs may partially function through AdipoR1. However, till date no exclusive receptors CTRPs has been identified. Identification and functional characterization of putative receptor and novel agonists for CTRPs may provide important insights that could lead to novel treatments for metabolic diseases.

Availability of data and materials
Because this is a review article, no individual data in any form is included inside the manuscript.

Ethics approval and consent to participate
Not applicable.

Consent for publication
All authors give their consent for publication.

Competing interests
The authors declare that they have no competing interests.

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