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Levels of different adipocytokines in chronic complications of type 1 diabetes mellitus

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Abstract

Type 1 diabetes mellitus (T1DM) is an autoimmune disease characterized by insulin deficiency which leaves patients dependent upon exogenous insulin administration. Chronic hyperglycemia presented in T1DM leads to the damage of blood vessels, causing nephropathy, retinopathy, neuropathy and cardiovascular diseases. Adipocytokines are hormones secreted by the adipose tissue and their main role is signalling key organs to maintain metabolic homeostasis. Adipocytokines are thoroughly explored in obesity and related metabolic disorders. Contrary, there is much less data concerning serum levels of different adipocytokines in T1DM patients, especially in the context of presence of different chronic complications of T1DM. Altered immunological system, chronic hyperglycemia, enhanced inflammation and oxidative stress, peripheral hyperinsulinemia accompanying subcutaneous insulin administration and possible excess in adiposity presented in T1DM patients can influence the secretion and modulate the action of adipocytokines. Their dysfunction causes dyslipidemia, stimulates further inflammation and accelerates atherosclerosis, thus contributes to the development of chronic complications of T1DM. In the same time, the existence of vascular damage presented in chronic complications of T1DM may have an influence on adipocytokines. Although the nature of the association between some of the adipocytokines and chronic complications of T1DM is relatively clear, further investigations in this field are warranted. This article is concentrated on reviewing available literature which has studied serum levels of different adipocytokines in the chronic complications of T1DM.

Introduction

Type 1 diabetes mellitus (T1DM) is a disease characterized by insulin deficiency due to the autoimmune destruction of pancreatic beta cells. It becomes manifest when remaining beta cell mass is not able to secrete sufficient amounts of insulin required for the maintenance of normal glucose homeostasis [1].

Adipocytokines are hormones secreted by the adipose tissue. Adipocytokines` main role is signalling key organs to maintain metabolic homeostasis and their dysfunction has been causally linked to a wide range of metabolic diseases [2]. Obesity is characterized by malfunction of adipocytokines` action, overproduction of inflammatory cytokines by adipocytes, increased infiltration of immune cells into the adipose tissue and chronic low-grade inflammation state [2]. Adipocytokines are thoroughly explored in obesity and related metabolic disorders, but there is much less data concerning serum levels of different adipocytokines in T1DM patients, especially in the context of presence of different chronic complications of T1DM. This article is concentrated on reviewing available literature which has studied serum levels of different adipocytokines in the chronic complications of T1DM.

Chronic complications of type 1 diabetes

Chronic hyperglycemia presented in T1DM patients leads to the damage of blood vessels, causing chronic microvascular (nephropathy, retinopathy and neuropathy) and macrovascular (cardiovascular) complications [3].

Diabetic nephropathy

Diabetic nephropathy (DN) is the leading cause of the end-stage renal disease in developed Western countries [4]. It is marked by the development of proteinuria and subsequent decline of glomerular filtration rate, which progresses over a long period of time [3]. Beside poor glycemic control, main contributor to DN development is elevated blood pressure [5]. Not only that DN leads to the end-stage renal disease but it also represents a major factor for the development of cardiovascular diseases (CVD) such as myocardial infarction and stroke in diabetes patients [6]. Changes in blood pressure both systematically and within the kidney occur early in diabetes and cause glomerular hyperfiltration which was initially postulated to be a major contributor to the damage of glomerulus and preglomerular vessels [7], although some recent data claims differently [8]. Other early changes in kidney of diabetes patients consist of hypertrophy of glomeruli, mesengial expansion, thickening of the glomerular basement membrane and growth of the proximal tubules [3]. As proximal tubule grows, glomerular filtration raises, kidney filters greater amounts of glucose, fatty acids, proteins and amino acids, growth factors and cytokines which are free to trigger various pathological pathways such as energetic imbalances, redox abnormalities, fibrosis and inflammation [3]. In large, changes in renal hemodynamics and in glomerular filtration barrier (mainly in glomerular epithelial cells) result in the advent of proteinuria [3]. As proteinuria progresses, glomerular filtration rate declines and DN develops to the end-stage renal disease. Slowing the progression of disease requires not only tight blood glucose control but also strict management of blood pressure and lipids.

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Diabetic retinopathy

Diabetic retinopathy (DR) is the leading cause of blindness among working-aged adults around the world [9]. It is characterized by a spectrum of lesions within the retina (changes in vascular permeability, capillary microaneurysms, capillary degeneration and excessive formation of new blood vessels) [3]. Clinically it is divided into nonproliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR), characterized by the growth of new blood vessels (retinal neovascularization). In the early stages, hyperglycemia causes intramural pericyte death and thickening of the basement membrane [10]. This leads to the changes in the integrity of retinal blood vessels, altering the blood-retinal barrier and vascular permeability [10]. The degeneration or occlusion of retinal capillaries results in ischemia which is followed by the release of angiogenic factors and the progression of disease into proliferative stage [3]. Neovascularization and macular oedema (accumulation of fluid within the retina which can occur both in NPDR and PDR) can cause the visual impairment [3]. In more severe cases, bleeding followed by distorting of the retinal architecture including the development of a fibrovascular membrane and retinal detachment can occur [10]. Nearly all patients with T1DM develop some retinal lesions after twenty years of diabetes duration [11], while the major vision threatening retinal disorder in this group of patients is PDR [12]. The risk of developing DR can be reduced by tight control of blood glucose, blood pressure and lipids.

Diabetic neuropathy

Diabetic neuropathy (DNP) is a syndrome which affects both the somatic and autonomic parts of the peripheral nervous system and it is a major factor in the impaired wound healing, erectile dysfunction and cardiovascular dysfunction in diabetes [3]. More than half of all patients with diabetes eventually develop DNP [13]. Disease progression was traditionally characterized by the development of vascular abnormalities (capillary basement membrane thickening and endothelial hyperplasia with forthcoming diminishment in oxygen tension and hypoxia) but recently there is some evidence suggesting that DNP selectively targets sensory and autonomic over motor neurons, with little vascular involvement [3]. Nevertheless, patients with developed DNP are experiencing numbness, dysesthesia, sensory loss and nighttime pain [3]. The loss of sensation in response to injury can lead to foot injuries, the development of foot and leg ulcers and consequent amputations [3]. Some patients can also develop a Charcot joint, a degenerative condition seen in weight-bearing joints, marked by bone destruction and deformity [3]. On the other hand, in case of autonomic nervous system impairment orthostatic hypotension, gastroparesis, nausea, bloating and diarrhea can develop [3]. All this disorders can dramatically worsen the quality of life of diabetic patients. The development and progression of DNP can be delayed mainly through tight blood glucose control.

Cardiovascular diseases

Diabetic patients are exposed to the increased risk of developing CVD. Individual with diabetes has the risk of myocardial infarction equivalent to that of non-diabetic person who has previously had a myocardial infarction [14]. CVD are responsible for more than half of the mortality of people with diabetes [14]. Diabetes increases the risk of myocardial infarction for three times compared to general population [15]. The development of CVD in absence of impairment of renal function is rarely seen in T1DM patients [8,16]. The major hallmark of diabetes is premature atherosclerosis which can result in the development of atherosclerotic plaque in coronary, carotid, femoral and other major arterial blood vessels, resulting in the progression of angina pectoris, myocardial infarction, stroke and peripheral arterial occlusive disease. Myocardium of diabetic patients can also be damaged in absence of hypertension and coronary artery disease and this condition is known as diabetic cardiomyopathy [17]. Diabetic cardiomyopathy is characterized by diastolic dysfunction which represents the inability of heart to relax and fill with blood during the diastolic part of cardiac cycle and this can result in the development of diastolic heart failure [3,18]. Causes of the accelerated atherosclerosis and myocardial damage in diabetes patients are mainly endothelial dysfunction (disbalance between vasoactive factors controlling its permeability, adhesiveness and integrity) [19], malfunction of vascular repair [20] and reduction in endothelial progenitor cells [20,21]. Beside strict management of blood glucose, blood pressure and lipids, anti-platelet agents are sometimes indicated in the prevention of the development of CVD in diabetic patients.

Adipocytokines

As it was mentioned beforehand, adipocytokines are hormones secreted by the adipose tissue and their main role is signalling key organs to maintain metabolic homeostasis [2]. Their dysfunction has been causally linked to a wide range of metabolic diseases [2]. In terms of their effects on the glucose metabolism, they can be divided into pro-hyperglycemic (resistin, retinol-binding protein-4, interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and other inflammatory cytokines) and anti-hyperglycemic (adiponectin, leptin, visfatin, omentin) adipocytokines [22]. In addition to this, they have very important role in the regulation of lipid metabolism, inflammation and atherosclerosis processes. The following text sets out basic facts about adipocytokines that are among the most frequently studied ones in T1DM patients: adiponectin, leptin, resistin, IL-6 and TNF-α.

Adiponectin

Adiponectin is the product of the adipose tissue and it acts protective on metabolic profile, vascular tonus and has anti-inflammatory properties [23,24]. Adiponectin exists as a full-length protein of 30 kDa (fAd) which circulates in trimeric, hexameric and higher order complexes [25]. A fragment containing the globular domain of adiponectin (gAd) has also been shown to exhibit potent metabolic effects in various tissues [26]. There are two different forms of adiponectin receptors (AdipoR): type 1 (AdipoR1) and type 2 (AdipoR2) [27]. AdipoR1 are ubiquitously distributed but are dominantly presented in skeletal muscles and have much greater affinity towards gAd, while AdipoR2 are expressed in liver and have affinity for both gAd and fAd [27]. Expression of both AdipoR1 and AdipoR2 increases after fasting and decreases after food intake [28]. Adiponectin levels decrease before onset of obesity and insulin resistance which clearly indicates that it is involved in the development of these disorders [29]. Levels of adiponectin increase with the improvement of insulin sensitivity, either as the consequence of a weight loss or usage of insulin sensitizing drugs [29,30]. Adiponectin inhibits platelet aggregation, decreases adhesion of monocytes in blood vessels and proliferation of vascular smooth muscle cells stimulated by vascular endothelial growth factor and increaes production of nitric oxide in endothelial cells [31-33].

Leptin

Leptin is a hormone secreted by the adipose tissue in direct proportion to amount of body fat, presumably to inform the brain regarding the quantity of stored fat [34]. Leptin signals nutritional

status to other organs especially the hypothalamus, which produces neuropeptides and neurotransmitters that modulate food intake and energy expenditure [35]. It also exhibits anti-diabetic effects independently of body weight and energy intake modulating actions [36]. Leptin also regulates hepatic lipogenesis and enhances muscle fatty acid oxidation [37,38]. Leptin has a structural and functional relation to inflammatory cytokines and acts pro-inflammatorily [39]. Persons with congenital deficiency of leptin are obese, and their treatment with leptin results in dramatic weight loss through decreased food intake and increased energy expenditure [40]. Also, leptin is successfully used to treat insulin resistance and hepatic steatosis presented in patients with congenital severe lipodystrophy [41,42]. Unfortunately, on the other hand, the most obese persons are resistant to the weight reducing effects of leptin as the consequence of existing leptin resistance. Leptin resistance is independently associated with insulin resistance and CVD in humans [40,43]. This way, although the original role of leptin in terms of metabolic disorders development is mainly protective, leptin resistance, which is typically registered in obese persons, turns leptin into the aggravating factor.

Resistin

Resistin is an adipocytokine produced mainly by macrophages in humans [2]. Studies on rodents have demonstrated that resistin contributes to hepatic insulin resistance and elevates blood glucose levels [44]. The physiological role of resistin may be maintaining blood glucose level during nutritional deficiencies, while its pathological effects seem to be associated with worsening of glucose utilization in a state of body fat excess [44]. Contrary, the suppression of resistin activity in rodents deteriorates adipogenesis and causes a subsequent increase in adipose tissue mass, followed by the enhancement in insulin sensitivity and glucose utilization [45]. Epidemiological studies have demonstrated the association of elevated circulating resistin with greater risk for increase of inflammatory markers, type 2 diabetes (T2DM), atherosclerosis and myocardial infarction development [2]. Also, recently, there is a growing interest in the role of resistin in the link between insulin resistance and malignant diseases [46].

Interleukin-6

IL-6 is a cytokine produced mainly by T cells and macrophages, but also by other cells like adipocytes and osteoblasts, and it acts in immune response and acute phase reaction [47]. Its level increases in the adipose tissue of obese mice and patients, but its role in glucose metabolism has not been fully resolved because of ambiguous results obtained from studies on animal models [2]. Although the IL-6 release from contracting skeletal muscle during exercise might mediate the beneficial effects (increased glucose uptake and fatty acid oxidation) [48] human studies show that increased serum IL-6 correlates with obesity and insulin resistance [49-51]. Studies which enrolled patients suffering from rheumatoid arthritis receiving monoclonal antibody against IL-6 (Tocilizumab) also show different results in terms of the impact on insulin sensitivity [2].

Tumor necrosis factor-α

TNF-α is a cytokine that is involved in systematic inflammation and stimulates the acute phase reaction. It is mainly produced by activated macrophages, but it also can be produced by many other different cells [52]. Initially, it was believed that the adipose-derived TNF-α was produced mainly by adipocytes, but data from animal models suggests that a significant amount of the adipose TNF-α is probably derived from macrophages and other immune cells [2]. TNF-α was the first cytokine identified in the adipose tissue of obese mice, which started an idea of metabolic inflammation concept [53]. The direct role of TNF-α in obesity induced insulin resistance was proved when it was observed that TNF-α treatment interferes with insulin signalling and blocks insulin actions [54]. Free fatty acids strongly stimulate TNF-α production in macrophages, and on the other hand, TNF-α stimulates lipolysis [55,56]. This cycle suggests that metabolic inflammation uses self-perpetuating mechanism to further its inhibition of insulin signalling and energy metabolism [2]. TNF-α also directly stimulates hepatic lipogenesis [57], and the adipose-derived TNF-α represents a major link between obesity and cancer [58]. Human studies demonstrated strong associations between circulating TNF-α and insulin resistance and other metabolic complications associated with obesity [59,60]. However, attempts to block TNF-α function in human subjects have not yet pointed out consistent metabolic outcomes [2].

Adipocytokines and chronic complications of type 1 diabetes

Adiponectin and chronic complications of type 1 diabetes

Adiponectin is the most studied adipocytokine in the context of presence of different chronic complications of T1DM. Although it is generally considered to be a protective molecule, increased concentrations of adiponectin in T1DM patients are independently associated with all-cause and cardiovascular mortality [61]. Most studies have shown that serum adiponectin is higher in T1DM patients than in nondiabetic individuals and in those with T2DM [62-67]. The reason might be the compensatory mechanism in which adiponectin responds to inflammation and oxidative stress [64,68-70]. Also, peripheral hyperinsulinemia as the consequence of subcutaneous insulin administration and chronic hyperglycemic state of T1DM may contribute to increased levels of adiponectin [65,66,68]. At the end, reduced clearance of adiponectin in patients with advanced renal disease also can be the reason for the elevation of adiponectin level [68,69]. The majority of studies have found that serum adiponectin levels are higher in T1DM patients with developed DN in comparison with normoalbuminuric patients [68-70] and that urinary adiponectin is the best independent predictor of DN progression in T1DM patients [71]. As far as DR in T1DM patients is concerned, clinical studies which have assessed its relation to serum adiponectin levels have shown ambiguous results [72,73]. There is a lack of the studies that have tried to establish the association between DNP and adiponectin levels but one of them has demonstrated that T1DM patients with developed DNP have higher levels of serum adiponectin [74]. Contrary, there is a great number of trials studying connection between serum adiponectin levels and CVD in T1DM. As it was mentioned before, increased concentrations of adiponectin in T1DM patients are independently associated with all-cause and cardiovascular mortality [61], although some trails have come to the opposite results [67,75].

Leptin and chronic complications of type 1 diabetes

While leptin is a target of many trials in T2DM patients, the number of studies assessing the significance of leptin in T1DM is modest. Various authors report different results regarding the serum leptin levels in T1DM in contrast to nondiabetic individuals. While some have come to the conclusion that levels have been increased [76-79], others have reported decreased levels [80,81], and the third have concluded that the levels have been unchanged [82,83]. Study conducted among young female T1DM patients revealed increased serum leptin levels in patients with developed DN in regard to normoalbuminuric patients

[84]. As far as for DR, there are no trials that have studied leptin exclusively in T1DM patients, but there is an evidence of increased intravitreal concentrations of leptin in patients with PDR [85,86], although others have drawn different conclusions [87]. Also, it has been demonstrated that leptin stimulates retinal neovascularization induced by ischemia [88]. Studies exploring the association between DNR and leptin exclusively in T1DM patients are missing but one that enrolled both T2DM and T1DM patients has shown increased levels of serum leptin in patients with developed DNP [89]. The relation between leptin and CVD in T1DM is poorly discovered. Studies attempting to establish the association between serum levels of leptin and indices of subclinical atherosclerosis have shown inconsistent results [90,91]. Nevertheless, understanding the real nature of the association between leptin and chronic complications of T1DM warrants further thorough and wide exploration.

Resistin and chronic complications of type 1 diabetes

As it is case for leptin, resistin has also been much more widely studied in T2DM patients. Similar to the findings of studies which have analyzed serum leptin levels in T1DM patients, trials assessing the level of serum resistin in T1DM patients in regard to nondiabetic subjects have come to contradictory results. While some investigators found increased serum resistin levels [90,92], others found its levels decreased in T1DM patients compared to nondiabetic subjects [44,93], and the third came to the conclusion that the levels were similar [94]. Unfortunately, there are no studies that have assessed the relation between serum resistin levels and the presence of different chronic microvascular complications in T1DM patients, but data from T2DM patients has shown increased serum resistin levels in subjects with advanced DR, advanced DN and DNP [95]. Also, data considering the association between serum resistin levels and CVD in T1DM patients is limited, but one of the studies has pointed out positive correlation between serum resistin level and carotid artery intima media thickness, surrogate of subclinical atherosclerosis [90]. Same as for leptin, understanding the real nature of the association between resistin and chronic complications of T1DM warrants further investigation.

Interleukin-6 and chronic complications of type 1 diabetes

Most of the studies analyzing the serum levels of IL-6 in T1DM have concluded that they are higher in the patients compared to the ones in nondiabetic subjects [96-100], while some of the investigators have found that levels are similar in two groups [101,102]. Although there is an evidence of increased IL-6 serum levels in T1DM patients with developed DN [103], others have found that they do not differ in regard to levels in patients without DN [104]. As far as DR is concerned, some studies report higher serum levels of IL-6 in T1DM patients with developed DR [105,106], while other investigators have found differences only in case of considering different degrees of retinopathy [104], and the third have concluded that there is no correlation between IL-6 serum level and DR [102]. One of the studies has demonstrated the correlation of increased IL-6 serum levels and autonomic neuropathy [107], while other has not found the difference in serum levels of IL-6 between T1DM patients without and with developed DNP [104]. There is a lack of trials that have studied exclusively IL-6 in context of CVD in T1DM, but one of them has pointed out correlation of IL-6 serum level and aortic pulse wave velocity, marker of arterial stiffness, which is the surrogate of subclinical atherosclerosis, but only in men [100]. Finally, inflammatory marker Z-score, which IL-6 is a part of, has shown strong and independent association with CVD in T1DM patients [108].

Tumor necrosis factor-α and chronic complications of type 1 diabetes

Some of the trials dealing with serum levels of TNF-α in T1DM report that they are higher in patients than in nondiabetic individuals [109,110], while other investigators have determined comparable levels in these two groups [111]. Serum TNF-α level was found to be associated with the fifteen year cumulative incidence of gross proteinuria in patients with T1DM [112], while other study has not found the difference in TNF-α serum levels in T1DM patients without and with developed DN [104]. TNF-α serum level is higher in T1DM patients with developed DR compared to the ones without this microvascular complication [106] and higher in T1DM patients with PDR in contrast to subjects without DR or with NPDR [113]. Some investigators found differences only in case of considering different degrees of retinopathy [104]. Previously mentioned study which enrolled both T1DM and T2DM patients has shown increased serum levels of TNF-α in those with developed DNP [89], while other study has not found the difference in TNF-α level in T1DM patients without and with developed DNP [104]. There is a lack of studies exploring solely TNF-α in regard to CVD in T1DM patients, but beforehand mentioned study proved an independent and strong association of inflammatory marker Z-score, which TNF-α also is a part of, with CVD in T1DM patients [108].

Conclusion

Adipocytokines are hormones secreted by the adipose tissue and their main role is signalling key organs to maintain metabolic homeostasis. Their dysfunction in T1DM patients can cause dyslipidemia, stimulate further inflammation and accelerate atherosclerosis, thus can contribute to the development of chronic complications of T1DM. In the same time, the existence of vascular damage presented in chronic complications of T1DM may have an influence on adipocytokines. Although the nature of the association between some of the adipocytokines, like adiponectin, IL-6 and TNF-α, and chronic complications of T1DM is relatively clear, further investigation, especially regarding the connection between leptin and resistin and chronic complications of T1DM is warranted. The development of different therapeutic agents which could selectively target and modulate the action of the adipocytokines may have the beneficial role in delaying the development of different chronic complications of T1DM.

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Authors contributions

Both authors have analyzed the literature, wrote and edited the manuscript.

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