

Adiponectin Secretion in HIV-Infected Subjects with or without Antiretroviral Treatment and Illicit Substance Use: Clinical Review and Update

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Received date: July 05, 2016; Accepted date: July 20, 2016; Published date: July 27, 2016

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Abstract

Adiponectin (Acrp30) is a novel polypeptide classified among adipokines that are chiefly secreted by adipocytes within adipose tissue. Besides the adipose tissue, levels of the adipocytokine also circulate in human plasma. Functionally, Acrp30 possesses a primary role in regulation of body fat stores with its anti-inflammatory, glucose and lipid metabolism and weight loss effects. Thus, circulating Acrp30 levels govern obesity and metabolic abnormalities including; dyslipidaemia, cardiovascular disorders and renal disease. A lipodystrophic syndrome including metabolic derangements are common features presenting in HIV-infected patients on antiretroviral therapy (ART). Decreased Acrp30 levels have been documented in lipodystrophic patients as a consequence of adverse effects attributable to various antiretroviral agents. Interestingly, Acrp30 levels are revealed to be suppressed in HIV-infected patients relative to healthy persons even prior to HAART commencement, indicative of HIV infection itself playing a role in Acrp30 dysregulation. On the contrary, circulating Acrp30 levels inversely correlate with body fat composition in healthy non-obese individuals. Thus, lowered Acrp30 concentrations are associated with weight accumulation in obese subjects. More importantly, illicit drug and substance use has been revealed to accelerate HIV disease progression while also impairing Acrp30 production within the adipose tissue. Consequently, these observations collectively portray Acrp30 as a metabolic correlate of adipose tissue inflammation and low fat store during episodes of HIV infection, lipodystrophic syndrome and illicit substance use. Therapeutic interventions should identify new approaches to restore Acrp30 production and supply during the aforementioned events.

Keywords: Adiponectin; Adipokines; Inflammation; Obesity; Metabolic abnormalities; Substance use; Lipodystrophy

List of Abbreviations:

Acrp30: Adiponectin; HAART: Highly Active Antiretroviral Therapy; HIV: Human Immunodeficiency Virus; NRTI: Nucleoside Reverse Transcriptase Inhibitor; NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor; InSTI: Integrase Strand Transfer Inhibitor; PI's: Protease Inhibitors; d4T: Stavudine; EVG: Elvitegravir; RPV: Rilpivirine; NVP: Nevirapine; EFV: Efavirenz; LPV/r: Lopinavir/ritonavir; PPAR- γ : Peroxisome-Proliferator Activated Receptor gamma; SREBP-1: Sterol Regulatory Element Binding Protein-1; C/EBP- α : CCAAT Enhancer Binding Protein alpha; FABP-4: Fatty Acid Binding Protein 4; TNF- α : Tumor Necrosis Factor alpha.

Introduction

The white adipose tissue constitutes a major endocrine organ that functions to produce biologically active substances termed adipokines, which exert either local and/or systemic effects [1-3]. Among these many adipokines includes; adiponectin, leptin, resistin, visfatin, adipsin, apelin, cheperin and retinol binding protein-4 (RBP-4) [2,4]. The adipocytokine, also known as adipocyte complement related protein (Acrp30) or gelatin-binding protein 28 (GBP-28); is a 30 kDa protein secreted exclusively from the adipose although some other tissues including the placenta are involved in its secretion [5,6].

Discovery of Acrp30 was through cDNA cloning techniques, with the adipocytokine being a protein product of apM1 gene that represents the most abundant adipocyte gene transcript [7].

Adiponectin modulates a number of endocrine-like and metabolic functions [8,9]. As such, reduction in circulating levels of Acrp30 is associated with obesity and cardiovascular disease [10], whereas higher levels are exhibited in obese individuals losing weight [11]. Hence, decreased production of adipokines by adipose tissue has been reported to predispose atherosclerosis and obesity-related pathological conditions including diabetes mellitus, endothelial dysfunction, cardiovascular disease and chronic kidney disease [12-14]. Contrastingly though, HIV-infected subjects with or without antiretroviral use display distinct profiles of Acrp30 expression relative to uninfected individuals. For instance, reduced Acrp30 levels have been documented in HIV-positive patients despite low fat mass [15]. Additionally, certain ART regimens are revealed to cause a decline in circulating Acrp30 levels [16].

The illicit substance using population accounts for a small group of individuals, yet responsible for high HIV burden globally [17-19]. The practice of illicit drug and substance use has been revealed to heighten systemic inflammation and immune activation especially during HIV infection [20-22]. However, complex interaction of illicit drugs and inflammatory profiles of metabolic derangement including Acrp30 has not been critically evaluated among HIV-infected illicit substance users. Although, a limited number of studies have shown illicit drugs

such as heroin to cause a dysregulated production of host circulating adiponectin levels [23,24].

Hence, all aspects put to consideration; there is accumulating evidence that Acrp30 serves multiple roles in striking the balance between glucose homeostasis/regulation and metabolic abnormalities both in normal and diseased states. This review compiles data from various research articles on Acrp30 expression and action particularly with emphasis on the adipocytokine kinetics including inflammatory responses during instances of HIV-infection, antiretroviral treatment and illicit substance consumption, which will be critical in understanding contribution of each agent towards systemic metabolic dysfunction, with a common aim of improving treatment outcomes for HIV-positive illicit substance consuming patients.

Regulation of adiponectin expression

Adiponectin an adipose tissue-specific protein is normally under transcriptional control of adipogenesis regulators comprising; PPAR- γ (peroxisome-proliferator activated receptor gamma), SREBP-1c (sterol regulatory element binding protein-1c), C/EBP- α , (CCAAT enhancer binding protein alpha) and ID-3 protein [25-28]. Receptors that serve to mediate effects of Acrp30 comprise AdipoR1 and R2 [29,30]. It is noteworthy that various anti-diabetes drugs more specifically thiazolidinedione (TZD) class to which pioglitazone and rosiglitazone (PPAR- γ agonists) belong, are characterized with Acrp30 high inducing capacity [31-33]. Therefore, increased Acrp30 expression modulates beneficial effects of this class of therapeutic agents.

More importantly, wide ranging post-translational modification which entails hydroxylation and glycosylation is critical for Acrp30 assembly and subsequent formation of functional oligomeric complexes [34-37]. Hence, following Acrp30 secretion that is regulated particularly by endoplasmic reticulum (ER) proteins ERp44 and oxidoreductase Ero1-La [38,39], the adipocytokine is found circulating freely within plasma in three oligomeric forms namely, high molecular weight (HMW; oligomer), medium molecular weight (MMW; hexamer) and low molecular weight (LMW; trimer) [40] (Figure 1). However, host circulating levels of this adipocytokine are dependent on various factors including sex, metabolic status and body fat distribution [41-43]. Additionally, the state of oligomerisation is vital as it regulates both signal transduction pathway and overall biological functioning of Acrp30 [34,36,44,45]). The three oligomeric complexes together are collectively termed as full-length adiponectin (fAd) [46].

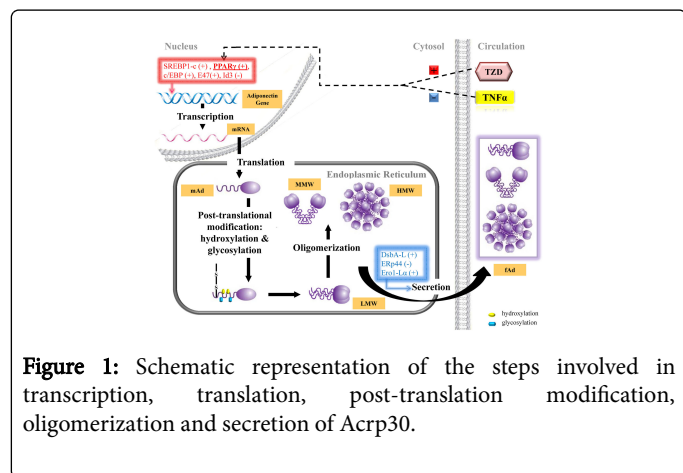


Figure 1: Schematic representation of the steps involved in transcription, translation, post-translation modification, oligomerization and secretion of Acrp30.

Several transcription factors (top left) which mediate adiponectin gene transcription are regulated to increase (thiazolidinedione, TZD) or decrease (tumor necrosis factor- α , TNF- α) adiponectin expression. Monomeric adiponectin (mAd) is post-translationally modified and further oligomerized to form trimers (low molecular weight, LMW), hexamers (medium, MMW) and oligomeric (high, HMW) forms. Various mechanisms (bottom right) mediate this oligomerization and secretion resulting in secretion of HMW, MMW, and LMW forms [47].

Adiponectin expression and action in non-obese/lean subjects

Normally, the circulating levels of Acrp30 show reciprocal relationship with the proportion of body fat composition [48]. Thus, low systemic concentrations of this adipocytokine have been described among obese subjects relative to their lean counterparts [49]. The subcutaneous adipose tissue (SAT) has been found to be associated with higher Acrp30 production compared to the visceral fat component of adipocytes [50]. Additionally, SAT accounts for roughly 85-90% of adipose tissue amongst lean persons. Therefore, these revelations may essentially justify the paradoxically higher levels of circulating Acrp30 reported amongst lean against obese subjects. Production of Acrp30 in lean individuals exerts effect on glucose metabolism through prevention of fatty acid mediated inhibition of glucose utilization by muscle cells [51], therefore minimizing the likelihood of obesity.

Adiponectin and obesity

Adiponectin has been shown to regulate multiple metabolic processes including glucose and lipid metabolism [52], hence fluctuations in circulating levels of this adipocytokine is implicated in various clinical challenges. For instance, decreased systemic Acrp30 levels that is experienced among obese subjects despite a high mass of adipose tissue is a driver for metabolic syndrome that is often characterized by dyslipidaemia, atherosclerosis, cardiovascular disease, endothelial dysfunction, insulin resistance (Type 2 diabetes) among others [10,53]. Hence, Acrp30 expression is observed to be under feedback inhibition during instances of obesity.

Immunologically, the inflammatory responses, more specifically a T helper-1 (Th-1) mediated pro-inflammatory milieu by tumor necrosis factor- α (TNF- α), is identified as a primary cause of suppressed Acrp30 expression in obese/diabetic subjects [54-56]. However, a rise in Acrp30 levels following weight reduction is demonstrated to lower TNF- α mediated inflammatory responses through activation of cAMP protein kinase A signaling pathways [57]. Likewise, over-expression of myelomonocytic cells has been shown to impair metabolic function in adipose tissue, although Acrp30 regulates this activity by inhibiting proliferation of these cells through apoptosis induction [58]. Overall, activity of these inflammatory mediators defines their role in promoting pathophysiology of obesity [59].

On the other hand, the precise mechanisms mediating development of atherosclerotic vascular disease among obese subjects remains largely undefined. However, Acrp30 levels become increased and localize within injured vascular walls as opposed to intact vessels which functions to suppress macrophage-to-foam cell transformation thereby regulating/inhibiting plaque build-up and resultant atherosclerosis [60,61]. These activities portray Acrp30 as a crucial

adipocytokine modulating anti-atherogenic effects besides counteracting the aforementioned adipose tissue inflammation.

Decreased Acrp30 secretion (hypo-adiponectinaemia) in obesity has been implicated with promotion of insulin resistance [62]; however, the underlying mechanisms modulating Acrp30 activity on insulin metabolism have not been well elucidated. Nonetheless, it has only been speculated that Acrp30 intensifies the expression of molecules that control fatty acid oxidation and energy dissipation within skeletal muscle thereby lowering triglyceride concentrations in this muscle [63]. Additionally, reduced fatty acid influx into the liver as well as gluconeogenesis is also shown to under control of Acrp30 [64] (Figure 2). To add further, more sub-physiological levels of insulin are produced within isolated hepatocytes to suppress endogenous glucose production [64,65]. Cooperatively, this accumulating evidence depicts circulating Acrp30 as an essential regulator of insulin sensitivity.

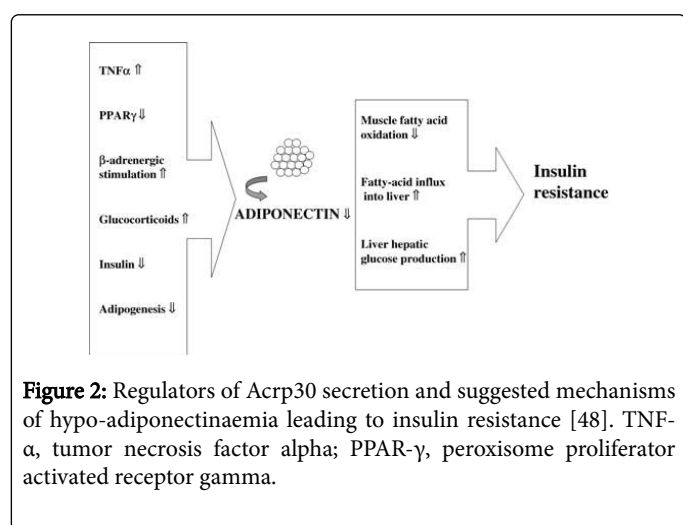


Figure 2: Regulators of Acrp30 secretion and suggested mechanisms of hypo-adiponectinaemia leading to insulin resistance [48]. TNF- α , tumor necrosis factor alpha; PPAR- γ , peroxisome proliferator activated receptor gamma.

Adiponectin in HIV-infected ART-naive subjects

Abnormalities in cytokine and hormone circulating levels, along with their altered metabolism have been observed in HIV infection [66,67]. As such, Acrp30 fails to maintain its inverse relationship with body fat mass during incidences of HIV infection [68], possibly due to adipocyte dysfunction resulting from the effects of HIV virus [69,70]. For instance, HIV-infected ART-naive subjects show considerable depletion of subcutaneous fat tissue which accounts for higher Acrp30 supply relative to visceral fat in humans [50,71]. However, the precise molecular mechanisms through which HIV inhibits Acrp30 production remain elusive, although studies suggest that HIV proteins, particularly protein R suppresses transcriptional activity of PPAR- γ , which is associated with regulation of Acrp30 gene expression in human adipocytes [72]. Altogether, these observations suggest that low fat store and underlying inflammation may regulate metabolic markers such as Acrp30 in HIV-infection.

Adiponectin in ART-experienced including, lypodystrophic patients

Human immunodeficiency virus infected individuals on HAART are reported to exhibit markedly reduced Acrp30 levels compared to uninfected persons [73,74]. This has been attributed to changes in adipocyte function with associated lypodystrophy and impaired fat redistribution effects [75,76], possibly resulting from the negative

adverse drug reactions of various antiretroviral agents [77]. Therefore, specific antiretroviral medications do exert influence on host plasma circulating Acrp30 levels. In particular, exposure to stavudine (d4T) treatment has been associated with lower plasma Acrp30 levels [16].

Likewise, Efavirenz (EFV), Elvitegravir (EVG) as well as rilpivirine (RPV) repress [78-80], whereas nevirapine (NVP) heightens Acrp30 release from adipocytes [79,81,82]. Interestingly though, some antiretroviral agents such as Maraviroc (MVC) an entry/fusion inhibitor, demonstrates no effect on expression and release of Acrp30 from human adipocytes [83], which may minimize adverse ART effect towards adipose tissue. Therefore, this has been suggested as a potentially beneficial outcome among emerging antiretroviral medication although studies are still ongoing to authenticate this. On the whole, peripheral fat loss and general lipodystrophic syndrome contribute immensely towards circulating Acrp30 dysregulation in HIV-1 infected antiretroviral treatment experienced patients (Table 1).

Drug	Class	Effect on Acrp30	Proposed Mechanism of effect	Author
d4T	NRTI	↓	Drug-induced mitochondrial dysfunction in adipocytes	[16]
EVG	InSTI	↓	Alters adipocyte differentiation and function	[79]
RPV	RPV	↓	Represses adipocyte differentiation causing impaired expression of main adipogenesis regulators including; PPAR- γ , SREBP-1 and C/EBP- α .	[81]
NVP	NNRTI	↑	Fails to impede adipogenesis but heightens expression of adipose regulators of SREBP-1, C/EBP- α and PPAR- γ .	[82]
EFV	NNRTI	↓	Disrupts human adipogenesis by down-regulating expression of associated marker genes including; FABP-4, PPAR- γ and C/EBP- α .	[78]
LPV/r	PI's	↓	Impairs adipocyte differentiation while reducing transcript levels of adipogenesis regulators comprising PPAR- γ and C/EBP- α .	[80]
MVC	FI's	None	Does not alter adipogenic differentiation in human adipose cells.	[83]

Note: NRTI: Nucleoside Reverse Transcriptase inhibitor; NNRTI: Non-Nucleoside Reverse Transcriptase inhibitor; InSTI: Integrase Strand Transfer Inhibitor; PI's: Protease Inhibitors; ART: Antiretroviral Therapy; d4T: Stavudine; EVG: Elvitegravir; RPV: Rilpivirine; NVP: Nevirapine; EFV: Efavirenz; LPV/r: Lopinavir/ritonavir; PPAR- γ : Peroxisome-Proliferator Activated Receptor gamma; SREBP-1: Sterol Regulatory Element Binding Protein-1; C/EBP- α : CCAAT Enhancer Binding Protein alpha; FABP-4: Fatty Acid Binding Protein 4.

Table 1: Classification of various ART regimens and their effects on Acrp30 production/levels.

Illicit substance use and adiponectin production

Multiple clinical studies involving both human and animal experimental models have previously established significant correlations between circulating Acrp30 levels and various-disease related outcomes including insulin resistance, cardiovascular and renal diseases [84,85]. However, Acrp30 expression in HIV-positive illicit substance consumers remains less well defined, although opium addiction has been demonstrated to have a positive association with

endocrine system disorders [23]. Nonetheless, substance abuse is an important co-morbidity factor that affects the outcomes of HIV clinical management [86].

Illicit drug and substance use has initially been shown to accelerate HIV/AIDS disease progression [22]. Equally, the practice is also reported to cause a dysregulation in cytokine production [87,88]. For instance, levels of circulating Acrp30 are revealed to be markedly reduced in frequently injecting heroin addicts [23,24]. Hence, drug and substance use suppresses systemic Acrp30 production perhaps through interference with kinetics and signaling pathways of the adipocytokine expression within adipocytes. Additionally, it's also possible that chronic inflammation associated with HIV-infection and illicit substance use promotes increased alterations in adipokine profiles of HIV-infected substance users.

Therapeutic role of adiponectin

A range of studies have demonstrated reduced Acrp30 expression to be linked to diabetes mellitus [89,90], while recovery of this adipocytokine controls insulin resistance by enhancing free fatty acid oxidation, glucose uptake and subsequent utilization [91]. Hence, diabetes medicaments including pioglitazone and rosiglitazone belonging to the TZD class of PPAR- γ agonists are observed to be potent inducers of Acrp30 expression [92-95]. This induction of Acrp30 has both metabolic and cardio-protective effects against diabetes mellitus and cardiovascular disease respectively. The proposed mechanisms that regulate Acrp30 expression by PPAR- γ agonists involves a reduction in triglyceride amounts within the muscle and liver cells as well as preventing adipocyte hypertrophy [63]. Additionally, it's also possible that TZD's heighten Acrp30 mRNA expression through the CCAAT/enhancer-binding protein sites [96]. Essentially, the high expression of Acrp30 is a fundamental mechanism of action that mediates beneficial effects of this diabetes controlling drug class.

Clinical trials involving administration of Acrp30 therapy on animal models controlled for obesity reveals hyperglycaemia and hyperinsulinaemia regulation without even inducing weight loss or gain in a number of this studies [48]. To add further, Acrp30 therapy has been demonstrated to reverse insulin resistance in mice manifesting obesity and lipoatrophy [63], which further potentiates the adipocytokine adoption among therapeutic interventions (Acrp30 replacement therapy) to be considered in HIV-infected lypodystrophic patients as well as obesity subjects during instances of metabolic abnormalities.

Conclusion and Future Directives

Summatively, findings from various studies portray Acrp30 as a critical surrogate marker indicative of numerous metabolic derangements including glucose regulation and fatty acid metabolism. However, future studies should identify and characterize the precise molecular mechanisms leading to altered glucose homeostasis during episodes of HIV infection, antiretroviral treatment and substance use. Additionally, more investigations are warranted in order to potentiate use of circulating Acrp30 levels in assessment of nutritional/metabolic profiles of both HIV-infected, treatment-naive and -experienced patients. More importantly, the role of illicit drug and substance use towards dysregulated production of circulating Acrp30, informs the need to assess drug use history among HIV infected patients with the overall goal of improving antiretroviral treatment outcomes in this population. On the whole, the interplay of signals regulated by Acrp30

defines its net effect as a modulator of metabolic inflammatory responses.

Conflict of Interest

The authors have no conflicts of interest to declare.

Authors' Contributions

All authors contributed in drafting, review of article and revising the manuscript. Final version of the manuscript was approved by all authors.

Acknowledgments

The authors thank Kenyatta University Post Modern library for availing space and permitting accessibility to online databases used to gather relevant information for this review. This work received no specific grant from any funding agency whatsoever.

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