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ORIGINAL RESEARCH

The dysregulation of adipokines in the synergy of diabetes and HIV infection

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Background: Dysregulated production or secretion of adipokines from adipose tissue may contribute to the pathogenesis of obesity-linked complications such as diabetes mellitus. Although adipokines have anti-inflammatory activity it is also capable of causing inflammation. Human immunodeficiency virus (HIV) infection predisposes an individual to the development of diabetes. Notwithstanding the side effects of antiretroviral therapy (ART), these may also exacerbate adipokine release and thereby promoting metabolic abnormalities.

Aim: This study reviews adipokines in the synergy of diabetes comorbid with HIV infection. It also examines the ameliorative action of ART on adipokines in diabetes.

Method: Multiple databases were used to search for each of the adipokines listed in the study. The role and expression of these adipokines were highlighted in its relationship to diabetes mellitus and HIV. Relevant articles were identified, selected and used to write this review article.

Results: This narrative review compares adipokine levels among HIV-infected and uninfected patients who are diabetic and have insulin resistance (IR). It also addresses the side effect of ART and its contribution to diabetes mellitus in HIV-infected patients. Adipokines are dysregulated in diabetes and insulin resistance, as well as in patients receiving ART.

Conclusion: Antiretroviral therapy, particularly protease inhibitors and non-nucleoside reverse transcriptase inhibitors, promotes IR and metabolic abnormalities. Nonetheless, obesity, physical inactivity, immune dysregulation and inflammation are also contributing factors to IR and diabetes mellitus in HIV-infected patients. Finally, circulating levels of adipokines are dysregulated in diabetes mellitus and further investigations are necessary.

Keywords: adipokines, diabetes mellitus, human immunodeficiency virus

Introduction

Diabetes mellitus (DM) is a metabolic disorder, characterised by an impairment of insulin production. Resultantly, the abnormal metabolism of carbohydrates elevates blood glucose levels. DM is classified into two main types. (i) Type 1 diabetes (T1D) is a congenital form characterised by deficient insulin production, and (ii) type 2 diabetes (T2D) which is an adult-onset condition characterised by high blood glucose due to either insulin resistance (IR) or a lack of insulin.[1] (See Table I.)

The International Diabetes Federation (IDF) reports a total of 572 million DM cases globally with 90% classified as type 2.[2] These statistics may not be an exact reflection of the status quo. Notably, DM is projected to escalate globally to 783 million cases by 2045 and is expected to be the leading cause of death. However, more than 50% of adults are unaware that they are living with DM. Four out of five diabetics emanate from low- to middle-income countries. In Africa, 24 million adults are diabetic with South Africa reporting 15.25% (11.07–19.95%) prevalence in adults.[3]

Table I: Clinical and biochemical data for T1D and T2D

Features	Type 1 diabetes	Type 2 diabetes
Age of onset	≤ 20 years	≥ 30 years
Body mass	Wasted to normal	Obese
Plasma insulin	Low or absent	Normal to high
Plasma glucagon	High, can be suppressed	High, resistant to suppression
Plasma glucose	Increased	Increased
Insulin sensitivity	Normal	Reduced
Treatment	Insulin	Dietary intervention, physical exercise, medication

The clinical symptoms of DM include polydipsia, polyuria, weight loss, weakness and susceptibility to certain infections.[4] High body mass index (BMI) and hyperglycaemia are ranked second and third, respectively, as the leading risk factors for DM development. The consequence of long-term DM is high

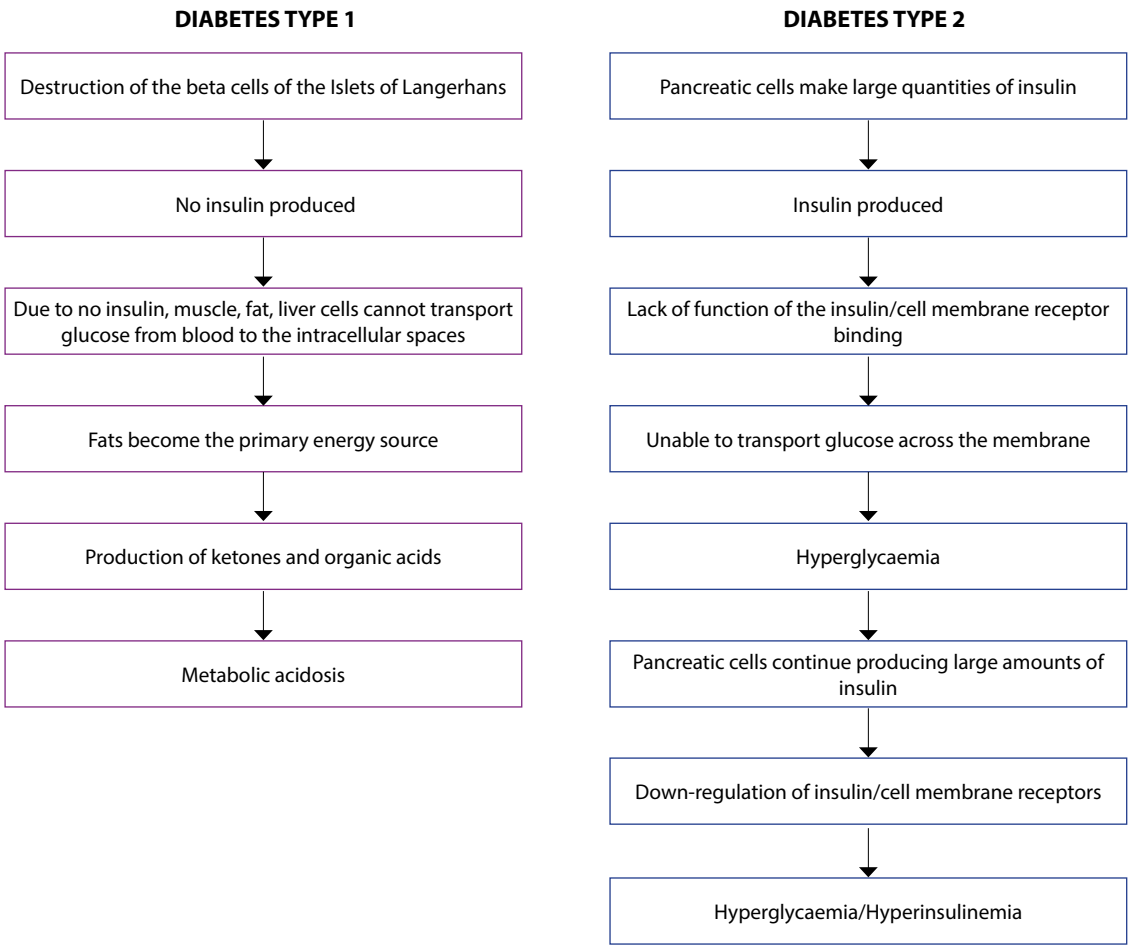

Figure 1: Sequence of events that occur in type 1 and type 2 diabetes[11]

mortality emanating from morbidity such as blindness, kidney failure, heart attack, stroke and lower limb amputation.[5]

HIV, infection, diabetes mellitus and antiretroviral therapy

South Africa is the epicentre of the global human immunodeficiency virus (HIV) pandemic.[6] Of note, 87% of T2D cases in South Africa are caused through either overweight or obesity. HIV-infected and acquired immunodeficiency syndrome (AIDS) patients frequently present with T2D. Moreover, lipodystrophy of adipose tissue and obesity occur in both treated and untreated HIV infection. Anthropomorphic changes of overweight or obese individuals occur with antiretroviral therapy (ART) initiation; and this predisposes HIV-infected patients four-fold to DM development compared to ART naïve patients.[7] This is a dilemma since most HIV-infected patients receiving ART fail to control glycaemic targets. It is therefore important to interrogate the lipodystrophy of adipose tissue in T2D together with adipokine regulation in patients receiving ART.

Insulin

Insulin and glucagon are antagonistic hormones that are secreted by the beta and alpha cells of the pancreas, respectively. These work together to regulate blood glucose levels. Insulin release is stimulated by high glucose levels (e.g. after eating) while glucagon release is stimulated by low blood glucose levels (e.g. during starvation). Insulin is responsible for decreasing blood glucose levels by promoting cellular uptake of glucose, thereby slowing down glycogen breakdown in the liver and promoting fat storage in adipose tissue. In contrast, glucagon increases blood glucose levels through the conversion of glycogen to glucose and the breakdown of fats and proteins into glucose.[8] The degree of insulin sensitivity determines glucose metabolism. As adipocytes store more fat molecules, these enlarge and release several products that modify the body's sensitivity to insulin. Free fatty acids and tumor necrosis factor-alpha (TNF-α) cause IR; while leptin, which regulates energy balance, is implicated in the development of insulin sensitivity.

Insulin and diabetes

The hyperglycaemia in T2D arises from defects in insulin secretion and IR by the liver and muscle tissue. This predominant type of diabetes is caused by a combination of genetic factors which is related to impaired IR, as well as environmental factors such as obesity, overeating, lack of exercise, stress as well as ageing.[9]

The autoimmune destruction of the beta cells in T1D leads to deficiency in insulin secretion with ultimate metabolic disarray,[9] as indicated in Figure 1. Therefore, in T1D, insulin production is compromised.

While T1D results from an autoimmune reaction to proteins of the islets cells of the pancreas, there is abnormal hypersecretion of insulin in T2D with contrasting impaired insulin function.[9]

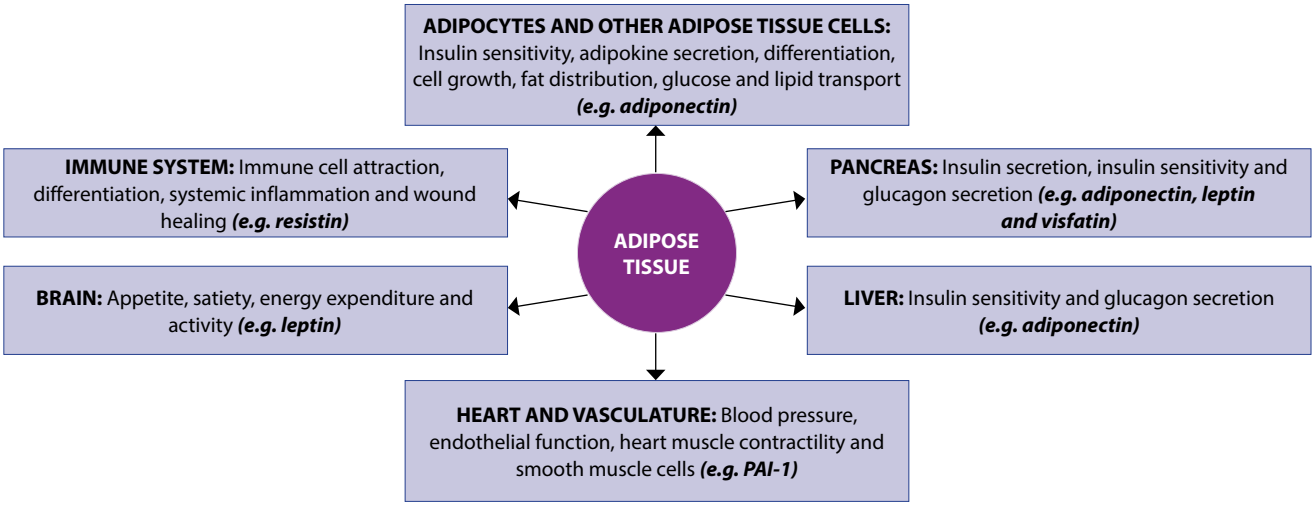

Figure 2: Adipose tissue and adipokine role in physiological processes[19]

Insulin and HIV infection

Long-term exposure to ART, specifically the protease inhibitors (PI), is associated with IR.[10] Shikuma et al.[10] proposed that factors such as obesity and physical inactivity, and immune dysregulation and inflammation also contribute to the increased prevalence of IR and DM in HIV-infected patients.

Type 1 diabetes occurs when there is no insulin production, which leads to metabolic acidosis. Insulin production occurs in type 2 diabetes; however, there is a down regulation of insulin/cell membrane receptors.

Adipose tissue

Adipose tissue is a large endocrine organ considered to be the site for the release of multiple adipokines.[12] Adipose tissue may be divided into two types: white adipose tissue (WAT) and brown adipose tissue (BAT). Majority of adipose tissue is WAT and is believed to be the site of energy storage, with an endocrine function in the secretion of hormones and protein factors; whereas the main role of BAT is non-shivering thermogenesis, particularly in human neonates.[13] Adipose tissue functions by influencing both glucose and lipid metabolism.[14] To mediate this function it releases adipokines, pro-inflammatory factors and free fatty acids, which impairs glucose metabolism, promotes the synthesis of toxic lipid metabolites and alters insulin signalling.[14] Since lipodystrophy of adipose tissue occurs in HIV infection, it is plausible that the dysregulated weight in the synergy of DM and HIV infection would exacerbate the opposing inflammatory state of both conditions, thereby affecting adipokine production.

Adipose tissue and HIV infection

HIV-infected patients on ART therapy tend to have fat accumulation and/or fat redistribution which is associated with altered adipose tissue homeostasis, differentiation and function that may ultimately lead to cardiovascular disease (CVD).[15] To date, there is a lack of clarity on the adverse effects of ART on the metabolic function but evidence implicates HIV infection.

Adipose tissue and diabetes

Studies have shown that fat distribution and visceral adipose tissue (VAT) accumulation lead to T2D in obese black South African women.[16] Prevention of T2D will require these individuals to reduce their weight by increasing fat loss. Further, subcutaneous adipose tissue (SAT) rather than VAT is the major contributor to IR in pre-menopausal black South African women.[17] Therefore, it is proposed that older women are at a greater risk of developing T2D than younger women emanating from the effects of menopause. However, VAT is also associated with poor lifestyle factors such as smoking, unhealthy diet and inadequate physical activity which promotes increased central obesity.

Adipokines

Adipokines, or adipocytokines, are cell-signalling proteins secreted by adipose tissue. Adipokines play a vital role in metabolism, energy homeostasis, weight regulation, inflammation and immunity (Figure 2 and Figure 3). Notably they act as orexigenic and anorexigenic hormones within the hypothalamus.[18]

Adipokines are also involved in co-ordinating a variety of biological processes as indicated in Figure 2 and Figure 3.[19] Adipokines that are affected in the duality of HIV infection and DM are ghrelin, gastric inhibitory polypeptide (GIP), plasminogen activator inhibitor (PAI-1), resistin and visfatin. Nonetheless, the role of insulin is elaborated upon due to its role in T2D.

Adipose tissue releases adipokines which have specific effects on the pancreas, liver, brain, immune system, and heart and vasculature.

Adipokines affect various physiological processes such as appetite and energy balance, insulin sensitivity, immunity, angiogenesis, inflammation and acute-phase response, blood pressure, haemostasis, and lipid metabolism.

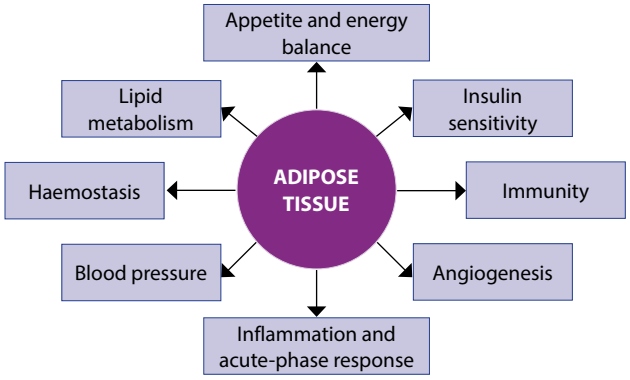

Figure 3: The function of adipokines[19]

Adiponectin

Structure

Structurally, adiponectin is a 244 amino acid long polypeptide with four distinct regions, viz. a short signal sequence that targets the hormone for secretion outside the cell, a short species-specific amino acid sequence, a 65 amino acid chain with similarity to other collagenous proteins, and a globular domain.

Function

Adiponectin has an insulin sensitising and anti-inflammatory function.[20] It functions in glucose regulation and fatty acid oxidation. Circulating adiponectin occurs in relatively high concentrations of 5–30 µg/ml and occupies 0.01% of plasma proteins. The levels of adiponectin are decreased in obese individuals compared to lean individuals.[20] According to Fasshauer,[21] adiponectin acts in the brain to increase energy expenditure and promote weight loss.

Adiponectin in diabetes

Adiponectin is associated with a reduced risk of T2D development.[22] Moreover, numerous clinical studies support an association between adiponectin levels and obesity-linked metabolic dysfunction.[20] Plasma adiponectin levels are decreased in patients with T2D. This suppression in patients with obesity and T2D, shows an inverse relationship with IR and visceral adiposity. Therefore, a high adiponectin level is associated with a lower risk of T2D development.[23] Other studies among healthy individuals and Pima Indians have shown an increase in plasma adiponectin.[24]

Adiponectin and HIV infection

The initiation of ART is associated with weight gain. This leads to impaired adipogenesis, adipocyte differentiation, and impairment of lipid and/or glucose metabolism, all of which culminate in cytokine dysregulation and chronic inflammation. Following ART, clinicians have observed body fat redistribution, IR, metabolic abnormalities as well as a change in body shape.[25] These abnormalities include a significant increase in circulating low density lipoprotein (LDL) as well as total cholesterol, triglycerides, glucose and a decrease in high density lipoproteins (HDL) levels.

Of note, protease inhibitors and nucleoside analogue inhibitors of viral reverse transcriptase play a major role in metabolic abnormalities. Treatment-naïve HIV-infected patients have suppressed adiponectin levels in contrast to patients receiving ART where there is gradual down regulation in adiponectin serum levels.[23] Since adiponectin is down regulated in both DM as well as in ARV-treated HIV-infected individuals,[23] it is plausible to expect an exacerbation of down regulation in the synergy of HIV-associated DM.

Leptin

Structure

Leptin is an adipokine-secreting hormone and the name is derived from the Greek word 'leptos' meaning 'thin'. In 1994, the human obese (OB) gene and its product, leptin, was identified and characterised. The OB gene is located on chromosome 7 (7q31.3) and consists of three exons and two introns straddling 18kb.[26] Leptin encodes a protein consisting of 166 amino acids with a putative signal sequence.[26] Only one OB mRNA (OBRb) occurs in abundance in human adipose tissue.[26]

Function

Leptin is secreted by adipose tissue in a pulsatile mode usually 2–3 hours after meals at a frequency dependent on the adipose tissue mass. Circulating leptin levels (normal range: 1–15 ng/ml) diametrically reflects the amount of energy stored in the adipose tissue. According to Robertson et al.,[27] people with congenital deficiency are obese. However, when treated with leptin, weight loss occurs due to decreased food intake.[28] Leptin levels in circulation reflects the amount of stored energy and guides the central nervous system (CNS) to maintain the ingestion of food and expenditure of energy accordingly.

Leptin influences food intake (Figure 5) through a direct effect on the hypothalamus, thereby functioning to reduce body fat mass in obesity. It regulates appetite by binding to Ob-receptors in the hypothalamus with consequential activation of several signal transduction pathways as indicated in Figure 4.[29] Leptin also performs its role outside of the hypothalamus where it interacts with chemicals and neurons that contribute to satiety.[27] Disturbances or defects in the leptin receptors (db/db) or the leptin gene (ob/ob) will result in prevention of leptin binding to the Ob-receptors which, in turn, will lead to deficiency in regulation of energy homeostasis, as well as regulation of both food intake and glucose homeostasis, due to resistance in insulin functioning and metabolic syndromes.[29] (See Figure 5.) Additionally, it is produced in the placenta, ovaries, mammary glands and liver. It is a pro-inflammatory cytokine that belongs to the type I cytokine superfamily and has structural similarity with interleukin 6. Notably, leptin levels decline with weight loss, which this leads to increased appetite and decreased energy expenditure.

Leptin functions in regulating thyroid hormone synthesis, insulin secretion, heart rate, bone mass, menstrual cycle, appetite, metabolism and energy homeostasis, as well as immune cell activation and blood pressure.[30]

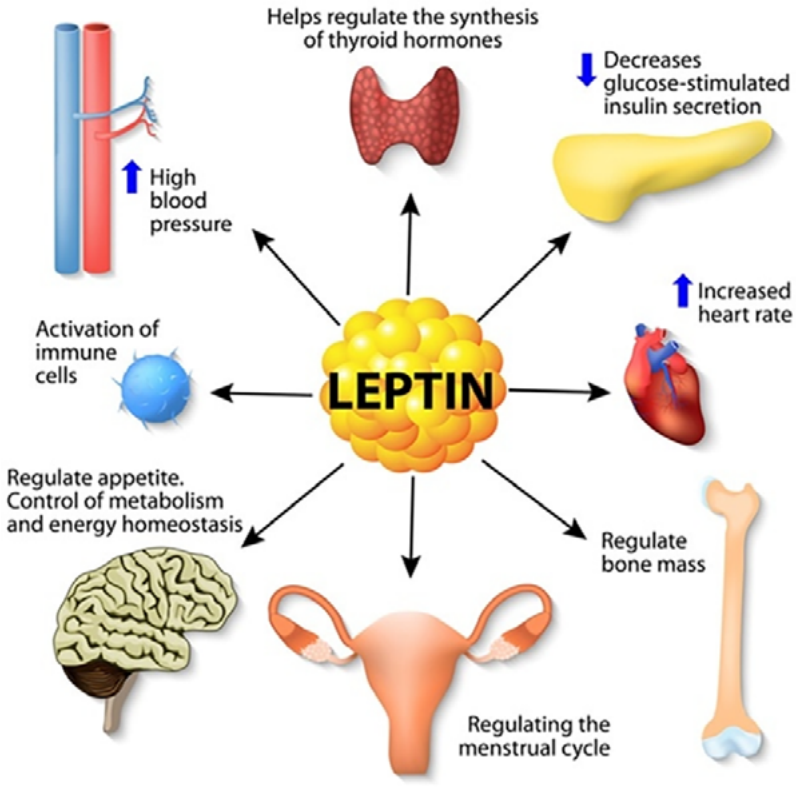

Figure 4: Functions of leptin[30]

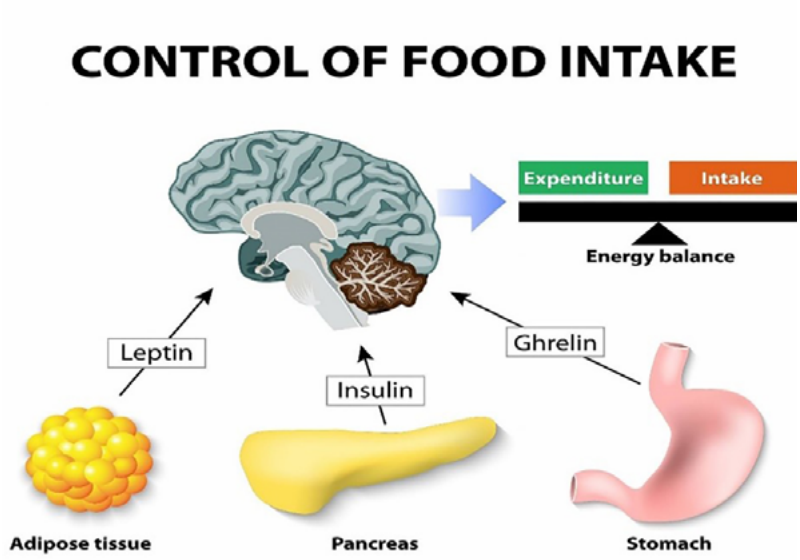

Figure 5: Leptin's control on food intake[31]

Energy balance depends on intake and expenditure. It is regulated by the stomach, pancreas and adipose tissue which release ghrelin, insulin and leptin, respectively, to signal the brain.[31]

Leptin and HIV infection

Tiliscann et al.,[32] in their study on leptin expression among HIV-infected patients on ART therapy, found that a large proportion of patients (41.1%) had hypoleptinemia. These abonormal leptin levels may be associated with ART-induced lipodystrophy, decreased insulin sensitivity and metabolic syndrome.[33] Also, HIV-infected individuals have less body fat than healthy individuals because of a reduction in SAT. Weight and BMI are thus lower in these individuals. Low leptin levels reflect reduced body mass and is associated with impaired immune function[34] which indicates that low levels of leptin in HIV infection exacerbates the immunodeficiency in AIDS patients.

Leptin in diabetes

Studies by Moon et al.[35] demonstrated an association between leptin and an increased risk of diabetes. Notably leptin replacement results in improved insulin sensitivity, homeostasis, and neuroendocrine and immune function. Although leptin plays a role in obesity due to leptin tolerance/resistance and obesity-related diseases, including T2D and CVD, leptin also mediates changes in adiposity or food intake and adaptive responses in systems like gastrointestinal, musculoskeletal and reproductive systems. Most patients with obesity and T2D have hyperleptinemia in response to leptin tolerance/resistance resulting in an impairment in the normal action of leptin.[36]

Ghrelin

Structure

Ghrelin is a hunger-stimulating peptide (also known as appetite-regulating hormone). It is a 28 amino acid peptide, acting as an endogenous ligand for the growth hormone (GH) secretogen receptor which is present on the somatotropic pituitary gland and specific hypothalamic neuronal cells.[37] Ghrelin is produced mainly by the cells lining the fundus of the human stomach and epsilon cells of the pancreas. Both acylated ghrelin (AG) and unacylated ghrelin (UAG) forms are found in circulation with a half-life of 10 minutes and > 35 minutes, respectively.[38] UAG accounts for approximately 50–90% of total ghrelin in circulation.

Unacylated ghrelin independently mediates specific biological functions while it shares other functions with AG.[38] Ghrelin affects metabolic function by influencing glucose homeostasis through the activation of insulin secretion and insulin receptor signalling, while insulin also influences circulating levels of ghrelin. Under physiological conditions, ghrelin acts as a regulator of energy balance to stimulate appetite and the storage of energy substrates while reducing energy expenditure during periods of limited food availability. When nutrients are abundant, ghrelin levels decrease to prevent the excessive accumulation of energy substrates.

Ghrelin in diabetes

Ghrelin regulates metabolic function in obesity-related conditions, such as IR and T2D. A study done on obese and non-obese children, as well as obese adults with or without IR or T2D, show that pre-meal total ghrelin levels were inversely associated

with insulin levels and the severity of IR.[39] Acylated ghrelin rather than UAG reduces insulin secretion while promoting IR in individuals with or without metabolic dysfunction. Although ghrelin has been known to function in glucose homeostasis, impairment in its secretion, caused by the ingestion of specific nutrients (high-fat consumption) or other genetic/environmental factors, could promote the excessive accumulation of lipids which could ultimately lead to IR and T2D.[38] Ghrelin influences the regulation of insulin secretion in healthy individuals. The intravenous administration of AG during fasting conditions reduces circulating insulin levels while increasing glycaemia. Furthermore, a study by Kiewiet et al.[40] reports that combined treatment with AG and UAG increased insulin sensitivity in morbidly obese patients. Insulin may reduce circulating ghrelin levels.[38] However, these authors had to isolate the effect of insulin and eliminate other factors that may also contribute to the decrease in levels of ghrelin. They used the oral glucose tolerance test (OGTT) and the euglycaemic hyperinsulinemia clamp (EHC). Reports show that there was reduced ghrelin levels in response to OGTT or mixed meals in healthy participants after 35 minutes. In this study, circulating ghrelin levels were decreased in response to insulin but not following the combined parenteral administration of insulin and glucose. Therefore, from these results a decrease in ghrelin levels is not directly mediated by insulin but through other mechanisms that require nutrients to transition in the gastrointestinal tract.[41]

Ghrelin and HIV infection

McFarlane et al.[42] noticed that ghrelin initiates the pathogenesis of metabolic disorders in HIV-infected patients by inducing hypertriglyceridemia, hypercholesterolemia, IR and DM. Ghrelin plays a role in elevating hypertriglyceridemia, thereby promoting the deposition of triglycerides in the liver of HIV-positive individuals. Studies have shown that there are decreased levels of ghrelin in lipodystrophy among HIV-positive patients, resulting in fat redistribution.[43] ART also contributes to low levels of ghrelin. A study by Mathonsi[44] on pre-eclampsia found that there were higher ghrelin levels in HIV-infected compared to uninfected women.

Gastric inhibitory polypeptide

Structure

Gastric inhibitory polypeptide (GIP) is a 42 amino acid glucose-dependent insulinotropic polypeptide which was first isolated from porcine intestine where it was shown to inhibit gastric acid secretion.[45] Owing to its inhibitory function, it was given the name gastric inhibitory polypeptide. This hormone was later found to be secreted by endocrine K-cells of the proximal small intestine (duodenum and jejunum) in response to feeding. It is known to be an incretin, an intestinal peptide that is secreted by the gut in response to dietary intake of glucose, lipids and carbohydrates.[46] GIP is known to stimulate a decrease in blood glucose levels by potently activating insulin release from the endocrine pancreas in a glucose-dependent manner following a meal to facilitate absorption of glucose and amino acids.[47]

GIP in diabetes

GIP is a physiological gut peptide secreted by the beta cell receptors and it is stimulated by a meal high in fats, which makes it a beneficial polypeptide due to insulin secretion which results in glucose metabolism. The downside of the secretion of beta cell receptors by adipocytes is that it results in insulin secretion and the promotion of fat storage.[48]

Introduction of fat or glucose into the duodenum evokes a five- to six-fold elevation in plasma GIP release. Excessive tissue fat storage leads to many pathophysiological conditions such as lipid deposition on the liver and muscle, obesity that ultimately contributes to IR and glucose intolerance, culminating in DM.[48] GIP has been confirmed as an obesity-promoting factor especially in those individuals with a high fat diet. It has also been confirmed that the deletion of the GIP-R signalling causes resistance to diet-induced obesity. Using a mouse model, they confirmed that the regulation of GIP-R signalling especially after fat intake is ideal to reduce obesity and T2D.

GIP and HIV infection

To date there is a paucity of data on GIP expression and HIV infection, ART, T2D and IR.

Resistin

Resistin is a cysteine-rich protein that is encoded by the resistin gene in humans. It is a signaling molecule expressed in monocytes, macrophages and adipocytes.[49] In adipocytes, resistin gene expression is induced during fat cell differentiation where it mediates an endocrine function. Resistin has been shown to increase transcriptional events that lead to an increased expression of several pro-inflammatory cytokines including, but not limited to, interleukin-1 (IL-1), IL-6, IL-12 and TNF-α.[50]

Structure

Resistin is a 12.5-kDa protein, containing 108 amino acids as a pro-peptide. Its hydrophobic signal peptide is cleaved before its secretion. Resistin circulates in the blood as a dimeric protein consisting of two 92 amino acid polypeptides that are linked by a disulfide bridge.[51]

Function

Resistin circulates at high concentrations in diet-induced and genetic varieties of obesity and has been found to modulate insulin action on hepatic glucose.[52] These proteins may be involved in the regulation of cell proliferation and differentiation. Nonetheless, given the production of FIZZ1/RELMα in inflammatory cells it is a possibility that its involvement in chronic inflammatory reactions may be associated with obesity.[53]

Resistin and diabetes

Falasca et al.[37] demonstrated that resistin is increased in T2D and is a potential link between obesity and IR. Notably, injection of recombinant resistin into mice reduces glucose tolerance and insulin action, whereas neutralisation with anti-resistin antibodies improves insulin action.[54]

Obesity induced by a high-fat diet, mutation of the leptin gene (ob/ob mice), or mutation in the leptin receptor gene (db/db mice) is associated with an increased circulating resistin concentration.[55] Resistin increases blood glucose and insulin concentration in mice. It also impairs the hypoglycaemic response to insulin infusion. Resistin suppresses insulin-stimulated glucose uptake in cultured 3T3-L1 adipocytes, and this effect is prevented by anti-resistin antibodies.[56] This data suggests that resistin provokes IR and that hyper-resistinaemia contributes to impaired insulin sensitivity in obese rodents.[54] The latter group also observed lower resistin mRNA in adipose tissue in a mouse model of obesity, viz. diet-induced obesity. Likewise, they observed hyper-insulinemia, hyperglycaemia, hypertriglyceridemia and hypertension in a rat model of obesity.

Additionally, Silha et al.[57] noted elevated resistin levels in obese and diabetic subjects while IR is noted in lean and obese subjects, although other studies have found no association between circulating resistin levels and IR.

Resistin and HIV infection

Increased levels of resistin have been found in HIV-infected individuals compared to uninfected individuals due to ART-related metabolic changes. Resistin is also implicated in early stages of atherosclerotic development in HIV-uninfected individuals. Further studies are required to assess the interplay between resistin and HIV-/ART-related cardiovascular disorders.

Visfatin

Visfatin is an enzyme/cytokine produced by adipose tissue during adipocyte differentiation and inflammation. Its production is regulated by glucocorticoids, TNFα, IL-6 and growth factors. Visfatin is responsible for the promotion of B cells which inhibit neutrophil apoptosis. According to Zulfıkaroglu et al.,[58] visfatin is involved in the regulation of glucose homeostasis since it has insulin-mimicking effects via the activation of an insulin receptor.

Visfatin and diabetes

Serum visfatin levels was shown to be higher in obese T2D individuals compared to non-T2D individuals (2.03 ng/ml vs 0.93 ng/ml, $p < 0.05$). This dysregulation of visfatin may reflect impaired biosynthesis implicating a possible role in the advancement of IR. Visfatin levels are proportional to visceral adipose tissue.[59]

Visfatin and HIV infection

Treatment with highly active ART (HAART) induces an increase of plasma visfatin provoking IR augmentation without a concomitant change in fat mass.[60]

Plasminogen activator inhibitor (PAI-1)

Plasminogen activator inhibitor (PAI-1) is a serine protease inhibitor (serpin) that functions as the principal inhibitor of tissue plasminogen activator (tPA) and urokinase (uPA), the activators of plasminogen and hence in the physiological breakdown of blood clots.

PAI-1 and diabetes

Higher levels of PAI-1 are noted in patients with no lipodystrophy or mixed forms, placing them at higher risk of cardiovascular disease. Freitas et al.[61] found that the lowest levels of PAI-1 occur in individuals with central fat accumulation. They concomitantly noted that PAI-1 concentration is increased in conditions with increased VAT and SAT, hypertriglyceridemia and hyperinsulinemia.

PAI-1 and HIV infection

HIV-infected individuals with fat redistribution show a significant elevation in PAI-1 level due to receipt of combination ART, as well as in patients with lipodystrophy and on cARV.

Summary

Adiponectin levels are dysregulated in metabolic disorders such as DM and reduced in obesity and HIV infection. Obese individuals may be treated with leptin to increase weight loss due to its effect on the hypothalamus which promotes a decreased craving for food intake. Ghrelin initiates IR and DM. It is decreased in obesity and up regulated in weight loss, causing muscle wasting; hence, it promotes the deposition of triglycerides in the liver in HIV-infected individuals. In patients receiving ART, ghrelin stimulates lipodystrophy. GIP-receptors secreted by adipocytes cause insulin secretion with subsequent fat storage, lipid deposition and resultant obesity, thereby enhancing IR and DM development. In obesity, circulating resistin is increased which regulates insulin action. Resistin is also increased in HIV-infected individuals compared to HIV-uninfected individuals. Moreover, ART correlate with observed metabolic change. Significantly increased levels of serum visfatin follow ART promoting IR. High levels of PAI-1 occur in patients with no lipodystrophy placing them at higher risk of CVD. Increased PAI-1 expression occurs among HIV-infected individuals with fat redistribution. Increased levels of c-peptide proteins are associated with increased CVD risk among HIV-infected individuals receiving ART.

Conclusion

Obesity and physical inactivity, immune dysregulation and inflammation contribute to the increased prevalence of IR and T2D. HIV infection and ARTs are implicated in lipodystrophy. This rearrangement of adipose tissue results in the dysregulation of adipokine production, promoting metabolic abnormalities and IR. Moreover, ART exposure also increases IR as well as metabolic abnormalities. This further exacerbates adipocyte differentiation, apoptosis and IR, subsequently aggravating systemic adipokine dysregulation.

Recommendation

Large group analysis of adipokines is required in mild, moderate and severe DM interfaced with stratification of duration and type of ART in order to conclusively interpret the effect of ART in DM comorbid with HIV infection. This will lead to better clinical management of the HIV-infected and uninfected diabetic patients. There is also a need for further research involving

specific under-investigated adipokines such as visfatin, c-peptide and PAI-1 in diabetes comorbid with HIV infection.

The side effects of ART include body fat redistribution, IR, metabolic abnormalities including increased LDL as well as HDL, triglycerides, glucose and cholesterol levels. Research in DM is required to correlate adipokines (ghrelin, gastric inhibitory polypeptides, glucagon, leptin, plasminogen activator inhibitor-1, resistin, visfatin and adiponectin) with the side effects of ART. The assessment of social factors as well as HIV parameters (CD4 counts and viral load) and drug interactions in conjunction with adipokine evaluation will provide a meaningful risk profile of both HIV-infected and HIV-uninfected diabetic patients.

Conflict of interest

The authors declare no conflict of interest.

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Ethical approval

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