REVIEW ARTICLE

HIV and Pancreas in the HAART ERA: Endocrinological Patterns

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ABSTRACT

Context Acquired immunodeficiency syndrome has become a pandemic disease since the very first cases were reported in 1981. Many studies estimate a prevalence of metabolic syndrome in 2-18% of human immunodeficiency virus patients. Other metabolic changes have been reported in human immunodeficiency virus infected patients under treatment with potent antiretroviral therapy. Recently, morphological changes on the islets of Langerhans were described in these patients. The objective of this study is a literature review in order to know the possible causes of endocrine disorders in these patients. **Methods** Bibliographic review of all indexed literature by searching the Medline/PubMed databases using the following keywords: human immunodeficiency virus, antiretroviral therapy, highly active, diabetes mellitus, insulin-secreting cells. **Results** Several published papers show endocrine alterations in patients using High Active Antiretroviral Therapy, but since these are multifactorial diseases such as diabetes and metabolic syndrome, a single explanation is weakened. **Conclusion** There are changes in the endocrine pancreas in acquired immunodeficiency syndrome in the High Active Antiretroviral Therapy era, both morphological as clinical, which can be attributed to several causes, including the High Active Antiretroviral Therapy.

INTRODUCTION

According to the World Health Organization, in 2013, there were approximately 39 million people living with HIV/AIDS worldwide. Of these, 3.2 million were children (<15 years). The WHO estimates that 2.1 million people became infected with the HIV virus in the world, a number that includes more than 240.000 children younger than 15 years **(Figure 1)** [1].

According to the latest epidemiological bulletin, since the start of epidemic in 1980, until June 2012, Brazil has had 656,701 AIDS cases registered. In 2011, were reported 38,776 cases of the disease, and the AIDS incidence rate in Brazil was 20.2 cases per 100.000 inhabitants, with the largest number of cases concentrated in the Southeast (56%) [2].

The UNAIDS (Joint United Nations Programme on HIV/AIDS) states that about 19 of the 35 million infected people are still unaware of the diagnosis. The sub-Saharan population is the most affected, comprising 71% of HIV cases (24.7 million people) in the world [3].

In risk populations, the screening strategy seems to be the most effective and cheapest in AIDS diagnosis. This finding suggests that in many health care settings, screening for HIV will provide important health benefits at a low cost, as well as earlier treatment [4].

The HAART therapy (High Active Antiretroviral Therapy), widespread since 1996, has been the recommended treatment for AIDS. It is a combination of drugs with different actions. They are divided into five classes: nucleoside reverse transcriptase inhibitors (NRTIs); Non-nucleoside reverse transcriptase inhibitors (NNRTIs); Fusion inhibitor (FI); Integrase inhibitor (II); Protease inhibitor (PI). The medicines are available gratuitously to all Brazilian citizens, provided by the Ministry of Health of Brazil [5-7].

- **NRTI -** act by competitive inhibition of HIV reverse transcriptase and may also be incorporated into the growing viral DNA chain, causing its interruption and thereby preventing the virus from reproducing. They are zidovudine, lamivudine, stavudine, abacavir, didanosine and tenofovir.

- **NNRTI -** bind directly to HIV reverse transcriptase, resulting in blockage of RNA and DNA dependent DNA-polymerase. The NNRTI binding site is located next to the NRTI, but is distinct from the latter. Unlike NRTIs, NNRTIs do not compete with nucleoside triphosphate nor phosphorylated triphosphate for their activity. They are efavirenz, nevirapine and etravirine.

- **FI -** act by inhibiting fusion of the virus with the host cell, thereby blocking virus entry: enfuvirtide.

- **II -** act by blocking the integrase enzyme activity, preventing the integration of viral DNA into the host cell DNA: raltegravir.

Figure 1. Summary of the AIDS epidemiology in the world in 2013 [1].

- **PI** - act in the final phase of viral replication, preventing the action of the protease enzyme in new proteins formed from RNA: saquinavir, ritonavir, indinavir, nelfinavir, lopinavir, atazanavir, fosamprenavir, tipranavir, darunavir.

Several adverse effects of HAART have drawn attention from the scientific community, most recently the disturbances in the metabolism of glucose and lipids, represented here as: 1. Peripheral insulin resistance; 2. Changes of fasting glucose and postprandial blood glucose; 3. Type 2 diabetes mellitus (DM); 4. Dyslipidemia; and 5. Disorders related to body fat distribution such as lipodystrophy [8, 9].

In this sense, in autopsy studies, Chehter *et al.* in 2014 [10], found morphological changes in the endocrine pancreas of patients who were taking HAART, specifically the pancreatic islets. These were changed in number and volume, and there were dysplasia-like changes in the nucleus of these cells, when compared to HIV/AIDS treatment-naive patients. This fact raised the issue on how specific morphological changes of the endocrine pancreas could be contributing to the development of type 2 diabetes mellitus or other complications **(Table 1)**.

OBJECTIVE

The aim of the study was to review the literature about changes of the endocrine pancreas in HIV patients under treatment with antiretroviral therapy is try to elucidate the morphological changes of the islets and found in autopsies. What are the possible causes for involvement of the endocrine pancreas in AIDS: antiviral therapy and/or its side effects? HIV infection? Metabolic syndrome?

METHODOLOGY

A literature review was carried out based on articles published in Medline/PubMed using the following keywords: HIV, HAART, type 2 diabetes mellitus, insulin-secreting cells.

Exocrine Pancreas and HIV

Pancreatic alterations in patients infected with HIV may occur from causes unrelated to AIDS, such as alcoholism, diabetes, cholelithiasis, adenocarcinoma, acute pancreatitis, chronic pancreatitis and medicines. On the other hand, AIDS-related causes include opportunistic infections and drugs used to treat AIDS. Such as asparaginase and azathioprine [11-15].

From the year 2000, Chehter [15] found particular pancreatic histological characteristics in patients who died from AIDS without antiviral treatment: reduction of zymogen granules in more than 50% of acinar cells, parenchymal atrophy in more than 60%, steatosis (60%) and nuclear abnormalities [2, 11, 15]. Thus, was determined the histological pattern of the pancreas in AIDS. A possible explanation was the pattern of protein calorie malnutrition due to malnutrition, weight loss and 'Wasting Syndrome' by associated factors, namely: anorexia, dysphagia, odynophagia, medication, neurological, diarrhea by pancreatic enzyme deficiency, increased muscle protein, hypermetabolism and increased cytokine. Patients are clinically asymptomatic, and the laboratory tests of function and image show a normal pancreas. It was observed that the Islets of Langerhans were fully preserved [14].

Regarding complications, few cases of pancreatitis were observed in this sample. Confirming this finding, in a multicenter study, acute pancreatitis was observed in only 5% of the HIV population studied. Yet, it found similar clinical among HIV patients and the general population, differing in relation to high rates of drug-induced pancreatitis (18%) and low incidence of biliary pancreatitis, as well as more complicated evolution and higher mortality [12-14].

Endocrine Pancreas and HIV

In a necropsy study, the finding of altered pancreatic islets in number and volume, and the dysplasia-like

Table 1. Main Antiretrovirals in HAART.

Groups	Drugs	Actions
NRTI	Abacavir, Didanosine Estavudine Lamivudine (3TC)	Act by competitive inhibition of HIV reverse transcriptase
	Tenofovir	
	Zidovudine (AZT)	
NNRTI	Efavirenz	Bind directly to HIV reverse transcriptase
	Etravirina	
	Nevirapina	
PI	Atazanavir	Preventing the action of the protease enzyme in new proteins formed from RNA
	Darunavir	
	Fosamprenevir	
	Indinavir	
	Saquinavir	
	Tipranavir	
FI	Enfuvirtida	Act by inhibiting fusion of the virus with the host cell
II	Raltegravir	Act by blocking the integrase enzyme activity, preventing the integration of viral DNA into the host cell DNA

NRTI nucleoside reverse transcriptase inhibitor; PI protease inhibitor; NNRTI non-nucleoside transcriptase inhibitor; FI fusion inhibitor, II integration inhibitor

changes in the nucleus of these cells, abnormally increased in patients treated with HAART, compared to naive patients [16], demonstrated there is more than one peripheral component (such as tissue insulin resistance insensitivity) determining a greater prevalence of type 2 diabetes mellitus or even impaired fasting glucose in those receiving antiretroviral treatment.

The morphological changes found raised the issue of a pancreatic function change in HIV patients, which led us to carry out a systematic review to check the possible correlations between the use of antiretroviral drugs, the metabolic syndrome and type 2 diabetes in this population, since the increased number of metabolic disorders is unquestionably related to an increased risk of cardiovascular disease [17].

Diabetes Mellitus

Hyperglycemia is the end point of a series of processes resulting in failure of pancreatic beta cells in secretion of sufficient insulin to maintain glucose levels within normal limits. The development of absolute or relative insulin deficiency is usually required for the manifestation of diabetes mellitus. The demand for insulin secretion is determined by the sensitivity of tissues to insulin for promoting glucose absorption. When there is resistance to insulin action, is necessary a compensatory increase in insulin secretion to allow the capture of normal glucose [18].

The failure of beta cells to secrete enough insulin may result from several factors, including genetic or programmed factors (suggested by family history of type 2 diabetes) or the toxic effects of high circulating lipids (lipotoxicity of beta-cells) [18]. Although insulin resistance and the prolonged hypersecretion by itself can only lead to impairment of pancreatic beta cells, various studies have provided evidence that HAART can directly impair insulin secretion [19, 20].

In 2009, Chandra *et al*. [21] demonstrated that the size of the pancreatic islets of mice treated with HAART was smaller in comparison to control rats, which is contrary to the finding of Chehter *et al*. [16] This effect can be attributed to the direct action of the PIs in the pancreas, causing toxicity to it. Another explanation for this discrepancy may be the exaggerated stimulation for insulin secretion due to increased peripheral resistance, which eventually causes deterioration or increase of the islets. This conflict shows that the experimental studies could not help us to solve this problem.

A prospective study of Brown and col. in 2005 [22], demonstrated the development of DM in 10% of HIV-infected patients on HAART during the four years of follow-up, compared to 3% in patients without HIV infection. After adjustment for age and body mass index (BMI), this difference means an increase of at least 4 times the risk of developing diabetes. When the prevalence of metabolic abnormalities related to glucose (fasting glucose and measures after overload tests) is taken into account alone, this figure rises to 25-35%, especially in patients receiving combined antiretroviral therapy, which reinforces a strong influence of these medications on the glycemic-insulinemic balance of these patients [9, 23].

Metabolic Syndrome x HAART

Initially, a large portion of diabetes development was credited to metabolic syndrome, since many prospective and retrospective studies estimate a prevalence of metabolic syndrome between 2-18% for HIV-infected patients [8, 22, 24]. Several clinical studies [19, 25] and in vitro studies were conducted in order to unravel the pathophysiological mechanisms involved in DM, mostly credited to peripheral insulin resistance [8, 23, 26].

It has been shown that the PIs interfere with cellular retinoic acid binding to type-1 protein (CRAB-1), which interacts with the peroxisomal proliferator activated receptor (PPAR). Inhibition of PPAR induces insulin resistance and release of free fatty acids [27].

Protease inhibitors are also known to disrupt insulin signaling in a variety of cell systems, mainly through mitochondrial dysfunction, as a key to understanding the insulin insensitivity experienced by these patients [28-33]. Another mechanism proposed for the insulin resistance associated with protease inhibitors involves apoptosis of beta cells via the mitochondrial pathway, expressed as a translocation of cytochrome c, and activation of caspase-3 and -9 in INS-1 cells [34].

We can not forget that the patients with HIV/AIDS are living longer and better. So they can get fat, contributing for the metabolic syndrome.

Insulin secretion X HAART

In 2009, Samaras showed endocrine pancreas changes that play an important role in the genesis of glucose abnormalities found in patients under combination antiretroviral therapy regimen. Evidences point to a reduction of 25-50% in insulin secretion and pancreatic beta cell function [8]. We also found in the literature studies indicating direct effects of HAART in the modulation of insulin secretion by pancreatic beta cells [20, 21, 32, 35, 36].

In order to clarify the specific changes in the pancreas, in 2009 Chandra [21] carried out an in vitro study using rat INS-1 cell line (β cell clonal lineage - rat insulinoma cells) to determine the mechanism linked to the toxic effects of HAART in pancreatic islets. It was observed that exposure to HAART significantly decreased insulin secretion in INS-1 cells.

In the study of Chandra *et al*. INS-1 cells were treated for 24 hours with nelfinavir, zidovudine or efavirenz in a single regimen or in combination, with subsequent

Table 2. Summary of articles cited – study in humans.

Author, Year	Study Design (Humans)	HAART	Conclusions
Samaras, 2009 [8]	Study Review	PI NRTI NNRTI	Interpretation of available data indicates that patients with treated HIV infection are at increased risk of diabetes mellitus, in part contributed to by class-specific and drug- specific adverse metabolic effects, the effects of lipodystrophy, and the impact of the modern epidemic of obesity.
Calza, 2011 [9]	HAART x DM and MS	PI NRTI NNRTI	The pathogenic mechanisms leading to diabetes mellitus and metabolic syndrome in HIV-infected patients, data from the literature continue to be contradictory. Both HIV infection and antiretroviral drugs are probably involved, but their exact pathological role remains uncertain.
Barbosa, 2013 [16]	Pancreatic histology in died patients in HAART era	NRTI NNRTI PI	No pancreas lesions secondary to HAART.
Kiage, 2013 [17]	HAART X Cardiometabolic risk factors	Zidovudine, Lamivudine, Nevirapine, Efavirenz, Stavudine, and other	Short-term cART is associated with a cardioprotective lipid profile. Tendency towards insulin resistance regardless
Dubé, 2001 [19]	HAART X IR and abnormal B-cell function	Indinavir	Insulin resistance without augmented B-cells response may explain the hyperglycemia
Brown, 2005 [22]	HAART x DM	PI Ritonavir Saquinavir Indinavir Nelfinavir	Greater than 4-fold increase in the role of incident DM in HIV-infected participants receiving HAART compared whit HIV-soronegative
Samaras, 2007 [23]	HAART x MS	NRTI NNRTI	MS prevalence in HIV-positive adults was lower than reported for general population
Araujo, 2014 [24]	HAART x DM and IR	Efavirenz, and others	A lower prevalence of Insulin Resistance is observed in the current HIV infected patients with fewer risk factors and receiving newer antiretroviral drugs
Tebas, 2008 [26]	Revision Study	PI Nucleoside Analog Others Antiretrovirals	Optimization of antiretroviral treatment regimens for HIV-infected patients with or at increased risk for development of abnormalities in glucose metabolism is discussed
Lee, 2004 [27]	Revision Study	PI	PIs have also been shown to cause other disorders of glucose metabolism, including impairment of insulin secretion and increased endogenous glucose production
Shikuma, 2005 [30]	Revision Study	PI NRTI	The hypothesized role of mitochondrial dysfunction can be supported to underlie each factors: inflammatory changes induced by HIV, and effects mediated through NRTI- and PI-induced lipodystrophy).
Ekali, 2013 [38]	HAART x Cardiometabolic Disorders	Stavudine	HAART duration is associated with obesity, fat distribution, blood pressure and cholesterol levels in HIV-infected Cameroonians, but does not appear to significantly affect glucose metabolism.

HIV human immunodeficiency virus; NRTI nucleoside reverse transcriptase inhibitors; PI proteases inhibitor; NNRTI nonnucleoside reverse transcriptase inhibitors; DM diabetes mellitus; MS metabolic syndrome; IR insulin resistance; HAART higly active antiretorvial therapy insulin resistance; HAART higly active antiretorviral therapy

Table 3. Summary of the articles of the endocrine pancreas- experimental studies.

Author, Year	Study Design (Experimental)	HAART	Conclusions
Koster, 2003 [20]	PI x B-cell function	PI	PI may significantly contributed to the development of overt diabetes in patients who receive HAART for long periods
Chandra, 2009 [21]	HAART x Insulin Resistance	Nelfinavir Zidovudine Efavirenz	HAART may increase serum insulin levels by dysregulating the insulin production
Rudich, 2001 [28]	HAART x MS	Nelfinavir	18 h of exposure to nelfinavir results in increased basal lipolysis, an effect associated with reduced expression of perilipin, a protein thought to be important in the regulation of lipolysis
Schütt, 2000 [29]	HAART x Insulin Signaling	Indinavir	Effects of indinavir on initial insulin signalling could cause, or contribute to, the metabolic effects of human immunodeficiency virus-1 protease inhibitors
Apostolova, 2011 [31]	Study Revision	PI NRTI NNRTI	Mitochondria evidently play an important role in such events. However, management of mitochondrial toxicity during HAART remains a challenge.
Schütt, 2004 [32]	HAART x Insulin Secretion and Insulin Signaling	PI	A long-term exposure to PIs not only induces peripheral insulin resistance but also impairs glucose-stimulated insulin secretion from beta cells
Ben-Romano, 2004 [33]	HAAR x IR	Nelfinavir	Nelfinavir induces a defect in the insulin signalling cascade downstream of the activation of PI 3-kinase. This defect manifests itself by impaired insulin-mediated recruitment of Akt/PKB and PKC-ζ to the plasma membrane.
Zhang, 2009 (34)	HAART x B-cells Apoptosis	PI	Suggest that the effects of protease inhibitors on β-cells need to be considered when assessing glucose homeostasis or the development of diabetes in people living with HIV+ and taking HIV protease inhibitors
Hruz, 2006 (35)	Revision Study	PI	The insulin responsive facilitative glucose transporter GLUT4 is the first molecule to have been identified as a direct target of HIV protease inhibitors.
Zhou, 2006 (36)	HAART x Lipid Metabolism	PI	Individual HIV PIs have different effects on the unfolded protein response (UPR) activation and expression of key genes involved in lipid metabolism in hepatocytes. HIV PI-induced UPR appears to contribute to lipid dysregulation.
Neye, 2006 (37)	HAART x Insulin Secretion	PI	Ritonavir and Nelfinavir but not Indinavir directly interfere with B-cell electrical activity, $[Ca^{2+}]_c$, and insulin secretion by inhibiting currents that are necessary to provide counterions for charge compensation to allow Ca^{2+} influx during action potentials.

HIV human immunodeficiency virus; NRTI nucleoside reverse transcriptase inhibitors; PI proteases inhibitor; NNRTI nonnucleoside reverse transcriptase inhibitors; DM diabetes mellitus; MS metabolic syndrome; IR insulin resistance; HAART higly active antiretorviral therapy

comparison of the schemes. The treatment with nelfinavir individually showed a significant decrease in insulin levels, but neither zidovudine nor efavirenz had this effect. The results suggest that in combination, nelfinavir was the component that caused the most harmful effect on the pancreatic beta cells [21].

The in vitro evaluation of the insulin secreting cells was also able to record the decrease in beta-cell sensitivity to glucose, probably due to the reduced expression of GLUT-2 type receptors in this cell line, which reduces deflagration of the insulin secretion cascade [8, 20]. Ritonavir and nelfinavir have shown to cause changes in voltage-dependent potassium channels and anion channels that provide an alternative mechanistic explanation for these acute effects [37].

The HIV-1 protease inhibitors also have a direct effect on pancreatic beta cells in the decrease of insulin secretion when stimulated by in vitro glucose, as demonstrated by many researchers [20, 21, 32].

Ekali, in a study in 2013 with 143 patients who received first-line HAART (NRTI), stavudine and zidovudine, demonstrated that there were no changes in glucose metabolism, regardless of treatment duration, concluding that access to new drugs for treatment of HIV patients should reduce complications related to drugs. However, more studies are needed to better characterize these metabolic changes [38].

The summary of the articles in order of appearance in the article are in **Table 2** and **3**. **Table 2** shows the studies in humans and **Table 3** shows experimental studies.

CONCLUSION

The increased blood glucose found on patients using HAART is the consequence of various metabolic changes that result in lipoatrophy and increased insulin resistance rates. However, the increase in blood glucose to pathological levels is only possible through failure of beta cells in responding to the organism's need of increasing insulin secretion to maintain homeostasis.

The inability of beta cells to secrete enough insulin may result from several factors caused by medications used in antiretroviral therapy, as protease inhibitors or nucleoside reverse transcriptase inhibitors, such as glucose signaling deficiency in GLUT2 transporters.

With the highlighted changes in relation to increased compensatory insulin production to overcome the increased insulin resistance, the pancreatic islets are changed in number and volume, the same way as dysplasia-like changes in its core. These morphological alterations can induce changes in the islets functions? Would there be a correlation between the morphological changes and the function? Insulin production? Primary or secondary insulin resistance? Direct or indirect toxicity of HAART?

However, more studies are needed in order to establish a causal relationship between the drugs used with the count of Alfa, Beta and Delta cells and the Pancreatic Peptide, as well as their respective functions. The need for screening for diabetes during HAART should be discussed and also, how to prevent the development of diabetes in this population at an early stage of increased insulin resistance.

Conflicting Interest

The authors had no conflicts of interest

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