

# Endocrine and metabolic disorders in HTLV-1 infected patients

## ABSTRACT

Human T-cell leukemia virus type 1 (HTLV-1) infection is endemic in Japan and several countries in South America, Caribbean and Africa. Endocrine and metabolic disorders have been variably reported to be associated with human T-cell leukemia virus type 1 (HTLV-1) infection. Therefore, the aim of this article was to critically evaluate the current knowledge of the endocrine and metabolic disorders associated with HTLV-1 infection. The literature search used PubMed, Web of Science, and LILACS databases in the past 10 years, utilizing, in various combinations, the following keywords: HTLV-1, adult T-cell leukemia, diabetes mellitus, GLUT-1, osteoporosis, hypercalcemia, autoimmune thyroid disorders, diabetes insipidus, inappropriate antidiuretic hormone secretion; pseudohypoparathyroidism; pseudopseudohypoparathyroidism. The proven endocrine manifestations of the HTLV-1 infection are calcium disorders which occur in some patients with acute HTLV-1/Adult T-cell leukemia/lymphoma. The few reports about thyroid, parathyroid, antidiuretic hormone and diabetes mellitus are insufficient to prove a causal association with HTLV-1 infection. The evidence for an association between endocrine disorders and HTLV-1 infection in general, and in asymptomatic patients is lacking. Given all these uncertainties, the endocrine expression of the HTLV-1 infection composes a promising research line for understanding the pathophysiology of this infection.

**Keywords:** HTLV-1; adult T-cell leukemia; endocrine disorders; metabolic disorders.

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## INTRODUCTION

The human T-cell lymphotropic virus (HTLV) is a retrovirus classified into four types: HTLV-1, 2, 3 and 4.<sup>1,2</sup> Despite that 95% of the HTLV-1 infected individuals remain asymptomatic, this infection can cause syndromes such as adult T-cell leukemia/lymphoma (ATLL), HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP), polymyositis, arthritis and infective dermatitis.<sup>1-3</sup>

The HTLV-1 infection is endemic in Japan and several countries in South America, Caribbean and Africa.<sup>2,4-7</sup> The transmission pathways of HTLV-1 infection include vertical, parenteral and sexual transmission.<sup>2,7</sup> Risk factors associated with HTLV-1 infection include: hemotransfusion, low socioeconomic status, low education level, high-risk sexual behavior, anal sex, first sexual relationship before 18 year-old and having more than 3 sexual partners in life.<sup>7,8</sup>

Several studies have been evidencing association between HTLV-1 infection and endocrinopathies and other metabolic disorders such as autoimmune thyroid diseases, hypercalcemia, type 1 diabetes mellitus and pseudohypoparathyroidism.<sup>1,9-12</sup> Due to the importance of these disturbances in the clinical spectrum of the HTLV-1 infection, this study aims to review the current knowledge about the endocrine diseases related to the HTLV-1 infection.

## ENDOCRINE-METABOLIC DISORDERS ASSOCIATED WITH HTLV-1 INFECTION

### CALCIUM DISORDERS

#### Hypercalcemia and osteoporosis

Adult T-cell leukemia/lymphoma (ATLL) associated with the HTLV-1 infection is a neoplasia with an average survival of six months in the

## Authors

Cresio Alves<sup>1</sup>

Luciano Dourado<sup>2</sup>

<sup>1</sup>MD, PhD - Chief of Pediatric Endocrinology, Hospital Universitário Prof. Edgard Santos, Faculty of Medicine, Universidade Federal da Bahia.

<sup>2</sup>MD - Fellow in Pediatric Endocrinology, Pediatric Endocrinology Service, Hospital Universitário Professor Edgard Santos, Faculty of Medicine, Universidade Federal da Bahia.

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**Correspondence to:**  
Cresio Alves, MD, PhD  
Pediatric Endocrinology Service, Hospital Universitário Professor Edgard Santos, Faculty of Medicine, Universidade Federal da Bahia  
Rua Plínio Moscoso, 222/601, 40157-190, Salvador, Bahia, Brazil  
E-mail: cresio.alves@uol.com.br

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acute form.<sup>13-15</sup> It affects 5% of the patients, starting in the average age of 58 years-old.<sup>16-17</sup> In 70%-80% of the acute ATLL form, the patients develop the humoral hypercalcemia of malignancy (HHM), a paraneoplastic syndrome characterized by hypercalcemia, osteoporosis and osteolytic lesions.<sup>13-15,18,19</sup> This suggests that there should be released or expressed molecules in ATLL cells performing a crucial role in HHM etiology.<sup>20</sup>

The HHM of patients with acute ATLL is caused by mechanisms that act synergistically, affecting directly or indirectly the osteoclastic differentiation. The most studied mechanisms are: (I) receptor activator of the nuclear factor- $\kappa$ B ligand (RANKL); (II) osteoprotegerin (OPG); (III) parathyroid hormone-related protein (PTHrP); (IV) pro-inflammatory cytokines; (V) macrophage inflammatory protein-1 alpha (MIP-1 alpha); (VI) nonstructural viral protein Tax; (VII) viral envelope protein, Gp-4; and (VIII) metalloproteinases.

### **RANKL**

RANKL (receptor activator of the nuclear factor- $\kappa$ B ligand) is a surface protein, part of the superfamily of TNF (tumoral necrosis factor), which when bound to their receptors (RANK) expressed in the osteoclastic precursors stimulates its differentiation in mature osteoclast, increasing its bone resorption and causing hypercalcemia and osteoporosis.<sup>21</sup> Patients with ATLL and hypercalcemia present increase of the expression of RANK.<sup>14,18</sup> Thus, the invasion of the bone marrow by ATLL cells expressing RANKL in its surface induces osteoclastic differentiation causing hypercalcemia.

### **Osteoprotegerin**

Osteoprotegerin (OPG) is a soluble receptor from the family of the tumoral necrosis factor (TNF) produced by several types of cells, including osteoblasts. It acts as a decoy receptor by binding and neutralizing RANK and its effect in the differentiation and proliferation of the osteoclasts.<sup>22</sup> Studies *in vitro* have shown that OPG inhibits the osteoclastogenesis, blocking the bone resorption by mature osteoclast and promoting osteoclastic apoptosis.<sup>14</sup> Mice with increased expression of OPG are osteopetrotic<sup>23</sup> while animals with deficiency of OPG present osteoporosis.<sup>24</sup> Nosaka *et al.* suggest that the decrease in the production of OPG in patients with ATLL can be one of the pathogenic mechanisms of the hypercalcemia.<sup>18</sup>

### **PTHrp**

The PTHrP (parathyroid hormone-related protein) is a peptide that binds to PTH1R (parathyroid hormone-1 receptors) promoting osteoclastic resorption, suppression of the osteoclastic activity and increase in the calcium urinary resorption. Patients infected by HTLV-1 present elevation of the PTHrP levels, mainly those with ATLL and HAM-TSP.<sup>1</sup> Fukumoto *et al.* evidenced hy-

percalciuria and increase of urinary excretion of cyclic AMP in 10 patients with ATLL, suggesting that the hypercalcemia was caused by the chronic increased mobilization of calcium.<sup>25</sup> Studies of cellular lineages infected by HTLV-1 have disclosed the production of a factor that stimulated the activity of the adenylyl cyclase in osteoblastic membranes, being the mRNA (messenger RNA) from these cells homologous to the mRNA of the PTHrP gene.<sup>26,27</sup> A study with ATLL patients, normo or hypercalcemic, has revealed that a rise in the expression of the PTHrP gene is directly proportional to the population of leukemic cells.<sup>28</sup> The trans-activation of the promoter of PTHrP by the protein Tax from HTLV-1 virus seems to be one of the mechanisms of expression of the PTHrP gene in the infected cells.<sup>28</sup> The PTHrP also boost the production of pro-inflammatory cytokines, stimulating the synthesis of interleukin 6 (IL-6) by osteoblasts and IL-8 and TNF-alpha by non-osseous tissues, for example the immune system.<sup>20</sup> Although the PTHrP and its receptors are upregulated in the ATLL, HAM/TSP and asymptomatic carriers of HTLV-1, other host factors are necessary for an accentuated expression of this peptide.<sup>17</sup> As the PTHrP is not able to induce the differentiation of the precursor hematopoietic cells into osteoclasts and an association between their elevated serum levels and HHM is not always observed, this indicates that other mechanisms contribute to this process.<sup>18</sup>

### **Pro-inflammatory cytokines**

The interleukin 2 (IL-2) stimulates the production and secretion of PTHrP and the IL-5 acts synergistically with PTHrP in the development of hypercalcemia.<sup>29</sup> Other cytokines as TGF-beta (transforming growth factor-beta), TNF-alpha and IL-1 also increment the expression of PTHrP in a variety of tissues.<sup>29</sup> As some patients present hypercalcemia without cytokine elevation, it is implicit the participation of other mechanisms.<sup>30</sup>

### **MIP-1alpha**

The MIP-1alpha (macrophage inflammatory protein-1-alpha) is a chemokine that acts as a stimulating factor for osteoclasts and monocyte migration (precursors of osteoclasts), besides inducing the expression of RANKL in ATLL. Okada *et al.*, studying 24 patients with ATLL and hypercalcemia, found high levels of MIP-1alpha in all patients, comparing to the positive finding in only 3/37 patients with ATLL without hypercalcemia.<sup>30</sup> After chemotherapy, the decrease in the serum levels of calcium had a concomitant decrease in MIP-1alpha levels, supporting the role of this protein in the pathogenesis of hypercalcemia. Besides, osteoprotegerin and anti-MIP-1alpha antibodies inhibited the transformation of peripheral mononuclear cells into osteoclasts.<sup>30</sup>

### ***Viral tax protein***

The nonstructural viral protein tax is able to activate CREB (cellular transcription factor CRE-binding protein), which renders activation of RANKL by PTHrP, resulting in hypercalcemia.<sup>31</sup> The role of Tax in the pathogenesis of hypercalcemia in the ATLL is controversial. Studies *in vivo* with mice have not exposed accretion in the expression of Tax in these animals, suggesting that other factors influence the regulation of PTHrP.<sup>29</sup> On the other hand, Gao *et al.* have shown that Tax transgenic (Tax+) mice develop hypercalcemia, osteolytic lesions and increased osteolytic activity whose expression was attenuated by use of drug inhibitors of osteoclasts.<sup>32</sup>

### ***Viral gp46-197 protein***

Sagara *et al.* depicted that rabbits immunized with a HTLV-1 structural protein (gp46-197) died due to hypercalcemia after receiving a boost of this peptide.<sup>14</sup> They suggest that gp46-197 would be an antigen mimicry of the osteoprotegerin, blocking its action by sharing the same antigenic sites.<sup>14</sup> The infusion of gp46-197 in mice resulted in a decrease in bone growth and hypercalcemia, which was curbed by the concurrent use of osteoprotegerin.<sup>14</sup>

### ***Matrix metalloproteinases***

The matrix metalloproteinases (MMPs) are enzymes that act in the extracellular matrix contributing to the formation and remodeling of bones and cartilages.<sup>1,33</sup> Mice deficient in a type of MMPs (MT1-MMP) present severe defects in the development of the axial and appendicular skeleton and craniofacial alterations as a consequence of the decrease of the proliferation of chondrocytes in the growth plate.<sup>33</sup> Schachter *et al.* proposed that an infection by the HTLV-1 could deregulate extracellular matrix proteins and its tissue inhibitors leading to the development of osteoporosis in patients with HAM/TSP.<sup>1</sup>

## **PSEUDOHYPOPARATHYROIDISM AND PSEUDOPSEUDOHYPOPARATHYROIDISM**

Pseudohypoparathyroidism (PHP) is a term used to define a group of disorders characterized by resistance to the peripheral action of the parathyroid hormone (PTH). PHP is classified into IA (classical presentation), IB, IC, II and pseudopseudohypoparathyroidism.<sup>34</sup> Only three papers, indexed in MEDLINE, reporting the association between HTLV-1 and PHP, were published. The first depicted three cases of PHP in patients with juvenile onset of HAM/TSP.<sup>35</sup> Although all presented hypocalcemia, none of them had hyperphosphatemia. PTH was elevated in only one patient; none of them demonstrated increase of the phosphorus urinary concentration or cyclic AMP in response to the exogenous administration of PTH. In the second article, an additional 11 patients were depicted.<sup>12</sup> In this study, only

half of the patients had hypocalcemia, one had hyperphosphatemia and another, elevated PTH. The serum levels of 1,25(OH)<sub>2</sub> vitamin D were tested in three of seven patients. There was no report informing if those who had normal levels of vitamin D have been subject to reposition of this vitamin. The third article portrayed a patient with HAM/TSP and PPHP, without elevation of PTH.<sup>36</sup> What the patients in these articles had in common was a decline in the activity of Gsα in the membrane of erythrocytes and renal resistance to PTH, which is not enough to establish a diagnosis of PHP or PPH.<sup>37</sup>

The authors of these articles postulate that a possible mechanism for juvenile onset HAM/TSP is a state of immunodeficiency caused by deficiency of 1,25(OH)<sub>2</sub> vitamin D as a result of PHP.<sup>35</sup> Besides, they report that the HTLV-1 infection is not an inductor factor for PHP, but that PHP is a risk factor for a precocious onset of HAM/TSP in patients infected through blood transfusion, explaining this way the more precocious onset of HAM/TSP in these patients.<sup>12,36</sup>

## **THYROID DISORDERS**

### ***Autoimmune thyroid diseases***

Hashimoto's thyroiditis (HT) and Graves' disease (GD) are diseases characterized by humoral and cellular autoimmunity.<sup>38,39</sup> The retrovirus, being able to integrate in the cellular genome, can participate in the development of autoimmune disease, either through the expression of foreign antigens through alteration of expression of autoantigen or through the unbalance of subpopulations of serum lymphocytes.<sup>40-42</sup> Some evidences relate HTLV-1 infection as a possible pathogenic factor in the autoimmune thyroid diseases.

### ***Higher prevalence of seropositivity for HTLV-1 in patients with HT***

Kawai *et al.*, studying 144 patients with HT, found a higher frequency of seropositivity for HTLV-1.<sup>43</sup> In the same study, 33.3% of the HAM/TSP patients had evidence of HT, comparing with a 1.7% prevalence in the same region. Mizokami *et al.* found a higher HTLV-1 seropositive prevalence in individuals with HT and positive antithyroid antibodies.<sup>44</sup> Mine *et al.*, studying 1,019 blood donors found a stronger association between HTLV-1 seropositivity and the presence of antithyroid antibodies, when compared with seronegative controls.<sup>45</sup> Akamine *et al.* demonstrated a high prevalence of antithyroid antibodies in carriers of the virus and ATLL patients.<sup>10</sup> Lagaye *et al.*, studying patients with polyendocrinopathies, did not detect HTLV-1 antibodies through ELISA and Western Blot; but when *Southern Blot* and PCR methods were used, the viral DNA was detected in 35% of the patients.<sup>42</sup> Concerning to GD, Smikle *et al.* found a 6% HTLV-1 positivity for GD patients, comparing to a 4% seropositivity in healthy controls, which does not favor the association between HTLV-1 infection and GD.<sup>11</sup>

### Detection of viral products in the follicular cells of patients with autoimmune thyroidopathy

Kawai *et al.* found HTLV-1 viral proteins in thyroid tissue in HTLV-1 and TH patients<sup>46</sup> and, in another study, they detected the HTLV-1 viral protein gp46 in thyroid follicular cells indicating previous thyroid tissue viral infection and probable association between these two diseases.<sup>47</sup> Filho *et al.*, studying thyroid tissue from cadavers with GD and HT and normal controls, found 83% and 85% positivity for p19(gag) and gp21(env) HTLV-1 proteins, respectively, without any clinical evidence of HTLV-1 infection.<sup>48</sup> These findings did not confirm the role of HTLV-1 in the pathogenesis of thyroid autoimmunity, but suggest that they can be the result of cross reaction, molecular mimicry or endogenous retrovirogenesis.

### Detection of a higher viral load of HTLV-1 in patients with autoimmune thyroid diseases

Matsuda *et al.* found a higher HTLV-1 proviral load in the peripheral blood of patients with HT and GD comparing to asymptomatic carriers of the virus.<sup>49</sup> In this study there was no association between the proviral load and the titles of antithyroid antibodies. As the proviral load is a determinant factor for the development of the virus clinical manifestations it is possible that it takes part in the pathogenesis of autoimmune thyroid disease in HTLV-1 infected patients.

### Association between HTLV-1 infection and CTLA-4 polymorphisms

The CTLA-4 (cytotoxic T-lymphocyte antigen-4) is a molecule that decreases the immune response of T-cells, being implicated in the pathogenesis of autoimmune thyroid diseases.<sup>50</sup> Thus, polymorphisms of this gene could be associated with a higher positivity to thyroid diseases in HTLV-1 infected patients. Nevertheless, Tomoyose *et al.* did not find difference in the frequency of this polymorphism in patients with TH with or without positive HTLV-1 test, concluding that HTLV-1 infection is not regulated by CTLA-4.<sup>51</sup>

### Reports of autoimmune systemic manifestation of HTLV-1 associated with autoimmune thyroidopathies

Yamaguchi *et al.* described a higher prevalence of DG in patients with uveitis associated with HTLV-1.<sup>52</sup> Kawai *et al.* reported three patients with uveitis and arthritis related to HTLV-1 and Graves' disease, suggesting that this thyroid disease was associated with the viral infection.<sup>53</sup>

### HTLV-1 infection causing host immune derangement

Oh *et al.* reported that the HTLV-1 Tax protein downregulates FOXP3, a gene which codifies a fundamental protein for the development and function of the T-cells.<sup>54</sup> Mutations in FOXP3 results in alterations in subpopulations of regulator T lymphocytes, causing a primary immunodeficiency

syndrome called IPEX (immunodysregulation, polyendocrinopathy, enteropathy, X-linked), presenting multiple endocrine alterations, including thyroiditis and insulin-dependent diabetes.<sup>55</sup>

## CARBOHYDRATE DISORDERS

### Type 1 diabetes mellitus

Type 1 diabetes mellitus (T1DM) is a metabolic disorder caused by autoreactivity of T-cells resulting in destruction of beta cells in pancreatic islets. Viral infections are one of the mechanisms through which T1DM is triggered. Endogenous and exogenous retroviruses have been associated with the development of autoimmune diseases for its ability to integrate in the cellular genome.<sup>42</sup>

Concerning endogenous retrovirus, Conrad *et al.* have shown the presence of RNA sequences in the type K human endogenous retrovirus (HERV-K IDDMK1,222) in patients with T1DM raising the hypothesis that this virus would express a super-antigen able to trigger an immune T1DM.<sup>56</sup> However, Badenhop *et al.*,<sup>57</sup> Jaeckel *et al.*<sup>58</sup> and Muir *et al.*<sup>59</sup> did not demonstrate differences between patients with T1DM and healthy controls concerning the expression of this retrovirus. More recently, a study has shown that the HERV-K18 retrovirus, through its CD48 region, participates in the pathogenesis of T1DM.<sup>60</sup>

As for exogenous retrovirus, Lagaye *et al.* detected the presence of sequences of the region gag of the HTLV-1 in patients with polyendocrinopathies.<sup>12</sup> Nevertheless, the search for antibodies to HTLV-1 was negative in all patients. These findings lead the authors to speculate if the tested gag region would belong to only HTLV-1 or it would be a common site to other retrovirus, since other HTLV-1 genomic sites (pol e pX) were negative, not allowing to deduce a causal relationship between HTLV-1 infection and T1DM.

The only study about HTLV-1 and T1DM association was performed in Jamaica, describing a 17% seroprevalence of HTLV-1 comparing to a 4% seroprevalence in the control group.<sup>11</sup> The authors speculated if T1DM could be triggered by HTLV-1 infection. However, the small sample size and the fact that the control subjects were blood donors precluded data generalization. Other authors did not confirm these findings.

### GLUT-1 polymorphism

The transportation of glucose between the several compartments of the organism is mediated through the glucose transporters (GLUT).<sup>61</sup> Recently, it was shown that HTLV-1 use GLUT1 to infect T-CD4 (+) lymphocytes and polymorphisms in its gene could predispose some individuals to HAM/TSP, favoring the entrance of the virus into the cells, increasing its viral load and then its complications.<sup>62,63</sup> However, a recent study was not able to find association between genetic susceptibility to HAM/TSP and g.22999g > T, g.15339T > C and c.-2841A > T polymorphisms of GLUT1.<sup>64</sup>

## ANTIDIURETIC HORMONE DISORDERS

### Diabetes insipidus and inappropriate antidiuretic hormone secretion

Only four articles, published in Japanese and cited by Adachi *et al.*,<sup>9</sup> reported ADH disorders in HTLV-1 infected patients.<sup>65-68</sup> Two of these articles reported five HTLV-1 infected patients with central diabetes insipidus<sup>65,66</sup> probably by leukemic infiltration in the hypothalamus, thrombosis or infection in the central nervous system.<sup>9</sup> As hypercalcemia can be expressed through nephrogenic diabetes insipidus, it is important to rule out this possibility when investigating diabetes insipidus in patients with ATLL. Other

articles described two patients with the syndrome of inappropriate antidiuretic hormone secretion (SIADH).<sup>67,68</sup>

### RESEARCH PERSPECTIVES

Figures 1 and 2 summarize the possible physiopathologic mechanisms of the HTLV-1 associated endocrine disorders. Given the uncertainties of these associations, a theoretical discussion of research perspectives for the HTLV-1 and endocrine disorder associations is presented in order to stimulate works to fill the gaps of the current knowledge.

Figure 1: Mechanisms of hypercalcemia in HTLV-1 infection.

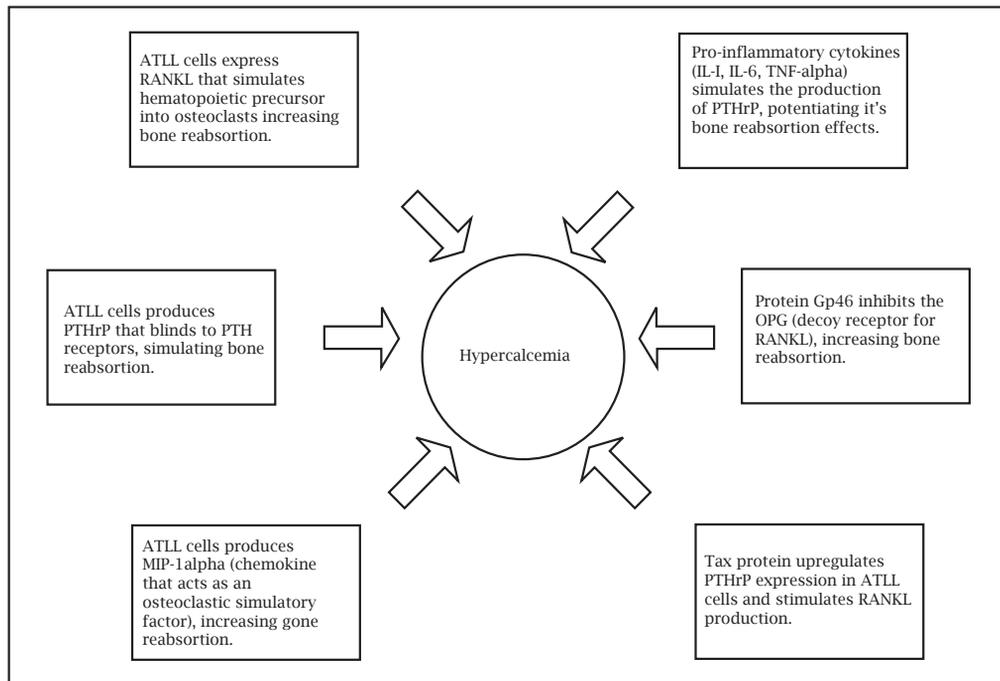
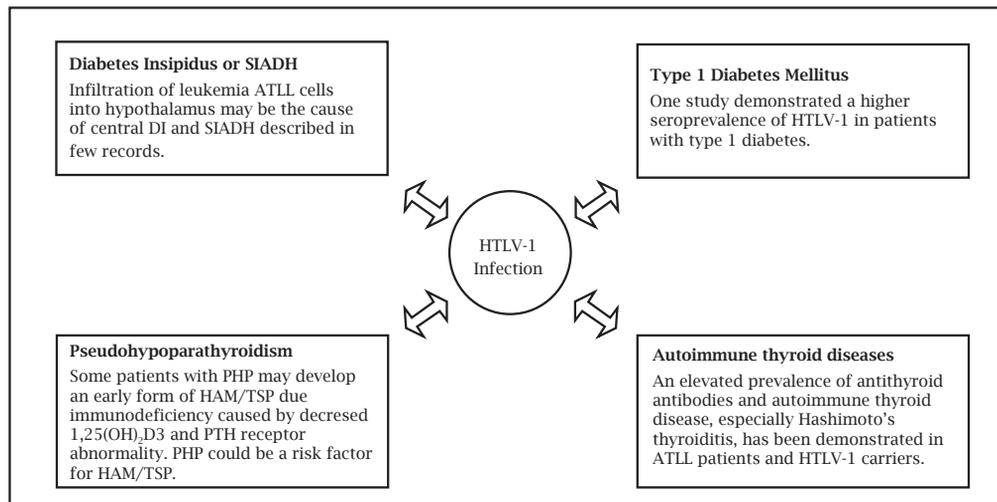


Figure 2: Endocrine disorders possibly associated with HTLV-1 infection.



RANKL, Receptor activator for nuclear factor- $\kappa$  B Ligand; ATLL, adult T-cell leukemia lymphoma; PTHrP, parathyroid hormone related protein; OPG, osteoprotegerin; MIP-1alpha, macrophage inflammatory protein-alpha; IL, interleukin; TNF, tumor necrosis factor.

## CALCIUM DISORDERS

### Hypercalcemia and osteoporosis

The identification of several mechanisms that lead to hypercalcemia in ATLL contributes to a better understanding of the metabolism of calcium and to studies aiming the application of new therapeutic agents to decrease the osteoclastic activity. For example, (I) osteoprotegerin (OPG): studies in mice with tumoral hypercalcemia showing a higher decrease in the serum calcium levels and an increase in the bone mass when these animals were treated with OPG when compared with the use of biphosphonates;<sup>69</sup> (II) estrogens: since estrogen levels decreases with aging; and as the estradiol raise the expression of OPG, maybe its reposition could be one of the therapeutic alternatives in individuals with ATLL and hypercalcemia;<sup>70-72</sup> (III) monoclonal antibody (denosumab) against RANKL: could block the osteoclastogenic actions mimicking the action of osteoprotegerin;<sup>73</sup> (IV) monoclonal antibody against PTHrP: a study showed that this therapy is able to block the function of PTHrP and reduce the calcemia in mice;<sup>74</sup> (V) MIP-1alpha: the therapy with MIP-1alpha can be other potential target to the treatment of hypercalcemia in the ATLL;<sup>30</sup> and (VI) biphosphonates: besides its antireabsorptive effect, this class of drugs has been shown exert antitumoral properties, limiting the growth of ATLL cells.<sup>75</sup>

### PSEUDOHYPOPARATHYROIDISM AND PSEUDOPSEUDOHYPOPARATHYROIDISM

The association between PHP and HTLV-1 is controversial and not proven. Thus more studies using more strict PHPIA and PPHP diagnostic criteria are necessary in order to: (I) study the activity of the  $Gs\alpha$  in patients with small stature without HAM/TSP and in patients with normal stature and HAM/TSP; (II) study other endocrine manifestations associated with  $Gs\alpha$  disorders; (III) verify the presence of hypovitaminosis D and its immunological collateral trigger of HAM/TSP; and (IV) evaluate the association between the precocious beginning of HAM/TSP in patients with PHP or PPHP who acquire HTLV-1 through blood transfusion.

## THYROID DISORDERS

### Autoimmune thyroid diseases

Although there is no study showing unequivocally a causal relationship between HTLV-1 infection and thyroid disorders, most of the studies support an association between them.<sup>41</sup> It is possible that individuals with a determined genetic predisposition to thyroid diseases have a higher probability to develop them when infected by HTLV-1, as the viral infection by itself is not able to

cause it.<sup>10</sup> Similarities between the viral and host protein sequence can induce a cross reaction and an immune response against thyroid tissues or a viral infection can activate a clone of autoreactive T-cells that would induce a thyroid inflammation. It is still necessary more studies to understand the role of HTLV-1 in the development of autoimmune thyroid diseases.

## CARBOHYDRATE DISORDERS

### Type 1 diabetes mellitus

Only one article was found in the medical literature reporting a higher HTLV-1 seroprevalence in patients with T1DM comparing to healthy controls.<sup>11</sup> Therefore, more studies are needed to confirm a possible role of the HTLV-1 infection as a trigger of T1DM or if the findings reported in a single study about the theme are attributed to a selection bias as the control group was assembled.

### GLUT-1 polymorphism

Although Costa *et al.* did not demonstrate mutations in three polymorphisms of the GLUT1, it is not possible to rule out the possibility of other polymorphisms implicated in the genetic predisposition to HAM/TSP.<sup>64</sup> Because of this, studies evaluating a larger number of polymorphisms are necessary to clarify this possible association.

## ANTIDIURETIC HORMONE DISORDERS

### Diabetes insipidus and inappropriate antidiuretic hormone secretion

Due to a small number of reports in the medical literature, more studies are necessary to prove a specific role of the HTLV-1 in the pathogenesis of these disorders or if these complications are only a result of a nervous system neoplasia or infectious aggression (ATLL immune suppression).

## CONCLUSIONS

This review shows that the HTLV-1 endocrine associated diseases are mainly calcium disorders, which occurs in a subgroup of patients with ATLL. Why only some of the patients with HTLV-1/ATLL develop hypercalcemia remains unanswered. The few reports about thyroid, parathyroid disorder, ADH and T1DM are scanty to prove a causal association with HTLV-1 infection. The evidence for an association between endocrine disorders and HTLV-1 infection, in general, and in asymptomatic carriers is lacking. Given all the uncertainties, the endocrine expression of the HTLV-1 infection composes a promising research line for understanding the pathophysiology of this infection.

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