UNIVERSIDADE FEDERAL DA BAHIA
FACULDADE DE MEDICINA DA BAHIA
PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA SAÚDE

Fatores de risco para arteriosclerose e disfunção erétil em indivíduos infectados pelo HTLV-1

Cassius José Vitor de Oliveira

Dissertação de Mestrado

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Fatores de risco para arteriosclerose e disfunção erétil em indivíduos infectados pelo HTLV-1

Cassius José Vitor de Oliveira

Professor-orientador: Edgar Marcelino

Dissertação apresentada ao Colegiado do PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA SAÚDE, da Faculdade de Medicina da Universidade Federal da Bahia, como pré-requisito obrigatório para a obtenção do grau de Mestre em Ciências da Saúde, da área de concentração em Urologia

Salvador (Bahia), 2015.

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Aqueles que têm um grande autocontrole, ou que estão totalmente absortos no trabalho, falam pouco. Palavra e ação juntas não andam bem. Repare na natureza: trabalha continuamente, mas em silêncio.

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EQUIPE DO SERVIÇO DE IMUNOLOGIA PARTICIPANTE DOS ESTUDOS EM HTLV-1

Anselmo Souza, biólogo

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Cristiano Sampaio, secretário

Dilma Simplício, técnica em laboratório

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Elisângela Novaes, secretária

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Glória Orge, psicóloga e bioquímica

José Abraão Carneiro Neto, urologista

Leilane Silva, enfermeira

Lúcia Passos, enfermeira

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Orlando Mário Sanches, técnico em laboratório

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Rosana Andrade, fisioterapêuta

Silvane Braga, bioquímica, imunologista

Thais Della Vechia, psicóloga

Valéria Bittencourt Gusmão, reumatologista

Victor Hugo, estudante de medicina

INSTITUIÇÕES PARTICIPANTES

UNIVERSIDADE FEDERAL DA BAHIA - UFBA

- COMPLEXO HOSPITALAR PROFESSOR EDGARD SANTOS
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Resumo:

AVALIAÇÃO DA RELAÇÃO DE DISFUNÇÃO ERÉTIL COM FATORES DE RISCO PARA ARTERIOSCLEROSE EM INDIVÍDUOS INFECTADOS PELO VÍRUS LINFOTRÓPICO HUMANO TIPO 1 (HTLV-1).

A disfunção erétil em indivíduos infectados pelo HTLV-1 tem forte associação com as disfunções neurológicas causadas por essa doença. Entretanto a principal causa de disfunção erétil na população geral é a arteriosclerose que leva a uma diminuição do fluxo sanguíneo no corpo cavernoso. O objetivo desse estudo foi avaliar se existe associação entre os fatores de risco para arteriosclerose com a disfunção erétil em indivíduos infectados pelo HTLV-1. Métodos: Estudo de corte transversal com indivíduos do sexo masculino infectados pelo HTLV-1 entre 18 e 70 anos sem história de câncer, sem uso de prótese peniana e sem déficit motor causado por outra patologia. Os indivíduos participantes do estudo foram classificados em dois grupos: um grupo com disfunção erétil e um grupo sem disfunção erétil. Esses grupos foram comparados e foi avaliada a relação entre obesidade, circunferência abdominal aumentada, dislipidemia, síndrome metabólica, diabetes mellitus e hipertensão arterial. Resultados: Dos 84 indivíduos selecionados 43 tinha disfunção erétil e 41 não. Houve relação da disfunção erétil com diabetes mellitus (P=0,03), idade acima de 60 anos (P=0,002) e o grau de disfunção neurológica (P<0,001). Dos fatores de risco para arteriosclerose avaliados em portadores de HTLV-1 houve relação da DE com a idade acima de 60 anos (P=0,024) com diabetes mellitus (P=0,01) e com a hipertensão arterial sistêmica (P=0,004). Odds ratio de 4,6 para idade acima de 60 anos, de 6,3 para hipertenção arterial sistêmica e de 22,1 para sintomático para HTLV-1. Conclusão: O comprometimento neurológico é a principal causa de disfunção erétil em indivíduos infectados pelo HTLV-1 e os fatores de risco para a arteriosclerose não tiveram forte relação com a disfunção erétil nesta população.

Palavras chave: 1- disfunção erétil; 2- Vírus 1 Linfotrópico T Humano; 3- arteriosclerose

Objetivo:

Correlacionar a disfunção erétil em indivíduos infectados pelo HTLV-1 com obesidade, dislipidemia, hipertensão arterial sistêmica, diabetes mellitus, síndrome metabólica e comprometimento neurológico do HTLV-1.

Introdução

O vírus linfotrópico humano tipo 1 (HTLV 1) é o agente causador da mielopatia associada ao HTLV-1 ou paraparesia espástica tropical (HAM/TSP) e do linfoma/leucemia de células T do adulto (ATLL)[1, 2]. Um elevado percentual de indivíduos infectados pelo vírus podem apresentar manifestações urológicas como disfunção erétil (DE) e bexiga neurogênica caracterizada principalmente pela hiperatividade vesical, urgência e urgi incontinência urinária[3-5]. Entre as prováveis causas de DE e de outras manifestações urológicas nesses pacientes estão as lesões neurológicas progressivas provenientes da infecção pelo HTLV-1 que são a dismielinização que afeta o cordão espinhal, e mielopatias[1, 6, 7]. Todavia embora exista uma relação entre a frequência de DE e o grau de comprometimento neurológico, cerca de 35,3% a 43% dos indivíduos infectados pelo HTLV-1 sem evidência de doença neurológica podem apresentar DE[3, 8].

A DE é um problema de saúde pública que afeta milhões de homens no mundo[9]. Na população em geral, a DE está muito relacionada a lesão vascular decorrente de arteriosclerose[10-13]. A arteriosclerose tem como fatores de risco o diabetes mellitus (DM), obesidade, hipertensão arterial sistêmica (HAS), dislipidemia e síndrome metabólica[14-17, 17, 18]. Os fatores de risco para a arteriosclerose estão presentes em até 92% dos casos de DE[19-22]. A arteriosclerose leva a fenômenos vaso oclusivos impedindo o fluxo sanguíneo adequado para as artérias penianas e para os microvasos do corpo cavernoso[23]. A obstrução das artérias penianas, secundária a arteriosclerose, ocorre devido a deposição de placas de ateroma gerando diminuição do fluxo sanguíneo nessas artérias levando a DE[24, 25].

A obesidade afeta 35% da população da população mundial[26]. A distribuição de obesos é irregular variando entre os países e as culturas[26]. No Brasil, a região nordeste tem cerca de 24% da população com o peso acima do esperado, sendo mais frequente em mulheres e em regiões urbanas[26-28]. Estudos demonstram que obesidade é um estado de inflamação leve crônica elevando os níveis de fator de necrose tumoral (TNF), interleucina (IL) - 6 e proteína C reativa (PCR) e essa elevação está diretamente associada ao aumento do índice de massa corpórea (IMC)[27, 29]. Obesidade é considerada um fator de risco independente para coronariopatias e DE, sendo que essa prevalência aumenta com a idade [12, 30]. A obesidade do tipo central, em relação às outras formas de obesidade, está muito associada a alterações metabólicas, diabetes e degeneração endotelial podendo levar a casos de isquemia cerebral e cardíaca[31]. Foi encontrada uma relação entre obesidade e DE nos pacientes com mais de 60 anos e entre o diâmetro abdominal maior que 102cm e DE nos pacientes acima de 60 anos[20]. Estudo anterior demonstrou uma associação entre DE e gravidade da DE com a circunferência abdominal[32].

Trabalhos avaliando o papel da dislipidemia na DE evidenciaram que os indivíduos com DE apresentam os níveis médios de colesterol total e de LDL mais elevados que os individuos sem DE[12]. O risco relativo de colesterol elevado e LDL elevado em relação a DE foi de 1,74 e 1,97 respectivamente[21]. Os níveis de triglicerídeos elevados[12] e a síndrome metabólica estão muito relacionados com o desenvolvimento de DE[33]. Todos os achado clínicos que levam a síndrome metabólica estão relacionados com DE e com a gravidade da DE[34, 35].

A DE, em pacientes portadores de HTLV-1, pode se manifestar como o seu primeiro sinal clínico[4, 5]. Os estudos que avaliam a DE em indivíduos infectados pelo HTLV-1 demonstram uma relação de DE com o grau de disfunção neurológica e com as manifestações urológicas como a urgência miccional, noctúria e aumento da frequência urinária[4]. Os pacientes com HAM/TSP apresentam uma prevalência de DE muito elevada podendo chegar a 100% dos casos[3]. Porém não existem estudos avaliando se outros fatores além do grau de disfunção neurológica podem contribuir para o desenvolvimento da DE em indivíduos infectados com HTLV-1. Não existem estudos avaliando se outros fatores causadores de disfunção erétil nessa população de indivíduos como a arteriosclerose, fatores hormonais ou fatores psicogênicos estão influenciando na disfunção erétil. Existe a necessidade de afastar se outras causas de DE estão servindo de fatores confundidores e não apenas o grau de lesão neurológica tem relação com a DE em indivíduos infectados pelo HTLV-1.

Diante do exposto, vários fatores além do envolvimento neurológico podem contribuir para a elevada ocorrência de DE em indivíduos infectados pelo HTLV-1. A nossa hipótese é que na infecção pelo HTLV-1 em adição a doença neurológica, obesidade, disfunção metabólica e aterosclerose podem contribuir para a ocorrência de DE.

Revisão da Literatura

Epidemiologia do HTLV-1.

A infecção pelo HTLV-1 acomete cerca de 10 milhões de pessoas no mundo e regiões do mundo como a África, Caribe, Japão, América do Sul e América Central tem uma elevada prevalência[36]. No Brasil, a cidade de Salvador na Bahia, apresenta a maior prevalência entre as capitais do estados brasileiros[37]. A principal forma de transmissão desse vírus é o contato sexual sendo que ele também pode ser transmitido pelo contato sanguíneo (através de transfusão de sangue, uso de seringas e agulhas contaminadas), transmissão vertical e o aleitamento materno[38-40]. Segundo as pesquisas a prevalência do HTLV-1 aumenta com a idade o que indica que a transmissão sexual é uma das principais formas de transmissão do vírus[41].

Patogênia e Manifestações Clínicas da Infecção pelo HTLV-1.

A infecção pelo HTLV-1 ocorre principalmente em células TCD4[42] porém macrófagos[43], células TCD8[42] e células dendríticas[44] também podem ser infectadas. As manifestações clínicas da infecção pelo HTLV-1 estão relacionadas com a elevada carga viral e a intensa atividade inflamatória decorrente da ativação excessiva do sistema imunológico causada pelo vírus[6]. Essa reação inflamatória exagerada estimula células T CD4, macrófagos e células T a produzirem mediadores inflamatórios como o interferon gama (IFN-γ), IL-6, CXCL9, CXCL10 e TNF[45, 46]. Existe uma relação direta entre os níveis séricos desses mediadores inflamatórios e o grau de manifestações clínicas da doença, porem alguns indivíduos assintomáticos também podem apresentar elevados níveis séricos desses mediadores inflamatórios[45, 46].

A infecção pelo HTLV-1 está associada a uma lesão neurológica inflamatória crônica progressiva que leva a mielopatia e pode causar uma serie de manifestações clínicas[46]. As manifestações clínicas do HTLV-1 puderam ser melhor compreendidas através de estudos epidemiológicos que comparam indivíduos infectados pelo HTLV-1 com indivíduos sem essa infecção revelando que além da mielopatia pode ocorrer xerostomia[8], dermatite[47], periodontite[8], hiperreflexia[8], polimiosite[48], artropatias[48], bexiga neurogência e DE[3]. A primeira associação do HTLV-1 com os sintomas neurológicos foi feita em 1985[49] e a HAM/TSP foi reconhecida pela Organização Mundial de saúde em 1989[50]. Os indivíduos infectados pelo HTLV-1 são classificados de acordo com as manifestações clínicas que apresentam podendo ser assintomática, oligossintomática ou provável HAM/TSP e cerca de 5% dos indivíduos infectados desenvolvem a forma clínica mais grave o HAM/TSP[51]. O HTLV-1 tem relação com a ATLL que é uma forma de leucemia de elevada letalidade que se manifesta através de um infiltrado celular na pele, trato gastrointestinal, fígado e pulmão[52]. A prevalência de ATLL em indivíduos infectados pelo HTLV-1 é de 6,6% para homens e 2,1% em mulheres respectivamente[52].

Disfunção Erétil na Infecção pelo HTLV-1

A DE em indivíduos infectados pelo HTLV-1 é um tema pouco estudado, não existem muitos artigos na literatura sobre esse tema, e suas causas ainda não estão bem esclarecidas e investigadas. Nos artigos que tratam sobre esse assunto é encontrada uma forte relação de DE com o grau de comprometimento neurológico causado pelo HTLV-1. Em um estudo a prevalência total de DE foi de 55,2% sendo que nos pacientes assintomáticos a prevalência foi de 35,9%, nos pacientes oligossintomáticos a

prevalência foi de 79,2% e nos pacientes com HAM/TSP essa prevalência chegou a 100%[3]. Nesse mesmo estudo também foi evidenciado a associação da gravidade da DE com o grau de lesão neurológica e a associação de DE com manifestações urológicas[3]. O HTLV-1 está associado com alta produção de citocinas inflamatórias porém em um estudo relacionando DE com os níveis séricos de citocinas inflamatórias como interferon gama e fator de necrose tumoral não foi encontrada associação entre esses fatores[53]. Todavia foi encontrada associação de DE com a carga proviral do HTLV-1 que é o principal marcador de evolução da doença[53].

Disfunção Erétil na População geral

Um estudo epidemiológico avaliando a DE no Brasil revelou que a DE atinge cerca de 53% da população[54]. Essa prevalência aumenta com a idade na população pois na população com menos de 40anos atinge cerca de 25% e na população com 70 anos ou mais pode chegar até 82%[54]. Os fatores associados com DE nesse estudo foram DM, HAS, hipercolesterolemia, doenças cardíacas, depressão, sedentarismo e tabagismo[54]. Sendo que dos fatores associados com a DE a DM apresentou a maior razão de chance 2,3[54]. Dos fatores avaliados atividade física apresentou fator de proteção para DE[54].

A DE na população geral está relacionada predominantemente com a arteriosclerose e a outras doenças causadas pela arteriosclerose como o infarto agudo do miocárdio, acidente vascular cerebral e doença arterial periférica[13]. Fatores de risco para a arteriosclerose como dislipidemia, obesidade[55], baixos níveis séricos de HDL, hiperglicemia, níveis elevados de triglicérides e síndrome metabólica estão relacionados com a DE[33], [56]. A obesidade central, que é medida pela circunferência abdominal, também tem relação com a DE[57]. Estudos utilizando ultrassonografia com Doppler medem a velocidade do fluxo sanguíneo nas artérias penianas e descrevem que a diminuição do fluxo sanguíneo nessas artérias causado pela arteriosclerose gera a DE[58]. Esse método foi descrito pela primeira vez em 1985[59] e consiste na injeção de substância vasoativas na circulação peniana para promover a vasodilatação e a medida do fluxo sanguíneo nesses vasos. As substâncias vasoativas mais utilizadas são papaverina, prostaglandina E1 e fentolamina que podem ser utilizadas isoladas ou separadamente[60]. O fluxo sanguíneo na artéria peniana medido pela ultrassonografia com Doppler acima de 35cm/s é considerado normal e o fluxo menor que 25cm/s é considerado baixo.

Fatores de risco para arteriosclerose tem grande relação com DE. Estudos apontam a obesidade como um fator de risco independente para a DE[61] inclusive em homens jovens[32]. Em relação a dislipidemia, níveis séricos elevados de colesterol total, colesterol LDL e níveis séricos baixos de colesterol HDL tem relação com a DE[21]. Outros estudos demonstram que além dos níveis séricos de colesterol níveis séricos elevados de triglicerídeos também tem relação com DE[62]. O DM pode apresentar relação com DE tanto pela questão do dano vascular em consequência da arteriosclerose como pela neuropatia diabética[63]. A HAS e os medicamento utilizados para tratamento da HAS também tem relação com a DE[21, 64]. O uso de medicamentos para tratar a HAS podem iniciar ou até piora a DE[21, 64]. A síndrome metabólica é um conhecido fator de risco para DE e abrange a presença de três de um total de cinco fatores de risco para a arteriosclerose no seu diagnósticos: níveis de pressão sanguínea elevado, níveis séricos de glicemia elevados, níveis séricos de HDL baixo, níveis séricos de triglicerídeos elevados e circunferência abdominal elevada[21, 56]. É descrito que quanto mais critérios diagnósticos de síndrome metabólica, maior é a chance de ter DE[65]. Mudanças no estilo

de vida, hábitos de vida mais saudáveis, como alimentação balanceada reduzindo a ingestão de calorias diárias, atividade física regular e perda de peso, redução do IMC estão relacionados com a melhora da função erétil e até a recuperação total da função erétil em alguns indivíduos que inicialmente apresentavam algum grau de DE[66]. Com essa melhora do estilo de vida além da melhora da função erétil ocorreu melhora dos níveis séricos de colesterol total, colesterol HDL, glicemia e triglicerídeos[66]. Na DE secundário a arteriosclerose é encontrada elevação de citocinas inflamatórias como TNF-α, IL-6, IL-8, IL-18 devido a uma inflamação crônica que gera a lesão endotelial[67]. Já foi descrito que esse estado de inflamação crônica está relacionado com a obesidade e que a perda de peso, diminuição do IMC, melhora da qualidade de vida leva a diminuição dessas citocinas[66, 67].

Disfunções hormonais como baixos níveis de testosterona total (TT) sérica estão relacionados com a DE na população geral. O nível sérico de TT considerado baixo ainda não está bem definido na literatura. Atualmente o valor sérico de TT abaixo de 8 nmol/L é considerado baixo, valores entre 8nmol/L e 12 nmol/L são considerados intermediários e acima de 12nmol/L são considerados normais segundo a recomendação da Sociedade Européia de Urologia e a Sociedade de Endocrinologia e Clínica Prática[68, 69]. A Sociedade Americana de Urologia recomenda que é considerado o valor baixo níveis séricos de (TT) abaixo de 10,4nmol/L[77]. Os indivíduos com níveis baixos de TT sérica são considerados com hipogonadismo e tem como sintomas DE, diminuição da libido, fraqueza, cansaço e desânimo[68, 69]. O hipogonadismo também pode se manifestar em indivíduos com valores intermediários de TT. É descrito na literatura que homens podem desenvolver hipogonadismo com o passar da idade, ganho de peso, obesidade e que esse hipogonadismo pode até ser revertido com a perda de peso, diminuição da circunferência abdominal e com hábitos de vida mais saudáveis[70]. O tratamento do hipogonadismo é feito com a reposição de testosterona[68, 69]. Estudos demonstram a associação de hipogonadismo com a DE e com a severidade da DE[71, 72]. Esses estudos além de avaliar o hipogonadismo com a DE fazem correlações do hipogonadismo com outros fatores de risco para a DE como a arteriosclerose[71, 72].

Fatores psicogênicos também estão muito associados com a DE e estão bem descritos na literatura[73]. Estudos apontam que os indivíduos com depressão tem uma chance maior de apresentar DE podendo chegar em 1,82[74] vezes maior em relação aos indivíduos sem depressão. Outro estudo descreve que os indivíduos negros e hispânicos tem mais DE relacionada a depressão do que os indivíduos brancos[73]. Além da depressão outros fatores de origem psicogênica são estudados como a confiança sexual e ansiedade de desempenho também estão relacionadas com a DE[75, 76].

Além da DE nos indivíduos infectados pelo HTLV-1 está relacionada a lesões neurológicas causadas pela doença[3] outras lesões neurológicas também estão relacionadas com a DE[77]. As lesões medulares completas e parciais, trauma crânio encefálico, acidente vascular cerebral, lesões neurológicas pós cirúrgicas, neuropatias periféricas são alguns exemplos de desordens neurológicas que estão relacionadas com a DE[78]. A DE ocorre nesses casos devido a interrupção do impulso nervoso secundário a alterações eletroneurofisiológicas que podem ocorrer nos neurônios ou nas sinapses nervosas causadas por essas patologias que podem estar relacionadas com o sistema nervoso central e periférico[79].

Na literatura só existem estudos que avaliem a associação da DE com o grau de disfunção neurológica em indivíduos infectados pelo HTLV-1. Não existem estudos

avaliando a associação da DE com arteriosclerose e com outras causas de DE em indivíduos infectados pelo de HTVL-1. A deficiência de artigos nesse tema e de informações sobre as causas da DE nessa população que estimulou essa pesquisa.

CASUÍTICA MATERIAL E MÉTODO

CARACTERÍSTICAS DA POPULAÇÃO DE REFERÊNCIA: Homens infectados pelo HTLV-1 com idade maior ou igual a 18 anos e menor ou igual a 70 anos.
DESENHO DO ESTUDO: Corte transversal, com dados coletados entre janeiro de 2013 e junho de 2015.
LOCAL: Ambulatório Multidisciplinar de HTLV-1 do Hospital Universitário da Universidade Federal da Bahia. Os indivíduos acompanhados neste ambulatório são provenientes de bancos de sangue, referidos de outros ambulatórios ou por pacientes do próprio ambulatório.
CRITÉRIOS DE INCLUSÃO: Homens infectados pelo HTLV-1 com idade maior ou igual a 18 anos e menor ou igual a 70 anos.
CRITÉRIOS DE EXCLUSÃO: Mulheres, histórico de câncer, uso de prótese peniana, presença de déficit motor por outra patologia.
TÉCNICA DE AMOSTRAGEM: Amostragem aleatório coletada por conveniência de acordo com a presença dos pacientes no ambulatório.
DIAGNÓSTICO: A documentação da infecção pelo HTLV-1 nesses pacientes foi feita pela técnica de ELISA (Cambridge, Birtek Corporation, Worcester, MA) e depois confirmada com Western Blot (HTLV-1 blot 2.4, Genelabs, Singapore).
DEFINIÇÃO DE CASO: Os indivíduos com exame positivo para HTLV-1 foram avaliados pela equipe multidisciplinar desta ambulatório sendo feita a avaliação clínica, neurológica e urológica nesses pacientes. O grau de comprometimento neurológico dos participantes foi avaliado por dois neurologistas usando a *Osame's Disability Motor Scale* (ODMS) e *Expanded Disability Status Scale* (EDSS)[80]. Os indivíduos com Osame=0 e EDSS=0 foram considerados portadores do HTLV-1. Os indivíduos considerados prováveis HAM/TSP foram classificados usando os parâmetros estabelecidos por Costa-Castro e colaboradores e apresentavam Osame=0 e com EDSS>0 e <2[81, 82]. Os indivíduos com Osame≥1 e EDSS≥2 foram considerados com HAM/TSP usando critérios estabelecidos pela Organização Mundial de Saúde[83] e por Costa-Castro[81, 82]. O *International Index of Erectile Dysfunction* (IIEF5) [84] foi usado para avaliar aunção erétil. É um questionário auto aplicado com variação de 0 até 25. Indivíduos com IIEF5 maior que 21 são considerados sem disfunção erétil. O IIEF5 também é capaz de medir a gravidade da DE: DE grave de 5 até 7, DE moderada de 8-11, DE leve moderada 11-16 e DE leve de 17 até 21. HAS foi definida pela história clínica dos pacientes ou quando indivíduos apresentavam pressão arterial sistólica maior que 130mmHg e ou diastólica maior que 85mmHg em mais de duas aferições[85]. **DM** foi definida pela história clínica dos pacientes e pela glicemia em jejum maior que 126mg/dl em mais de uma medida, glicemia duas horas após carga glicêmica de 75g de glicose maior que 200mg/dl e glicemia maior que 200mg/dl mais sintomas clínicos[86]. **Hipercolesterolemia:** valores de colesterol total maior do que 200mg/dl[87]. **Lipoproteinas de alta densidade baixo (HDL):** valores de colesterol HDL menores que 40mg/dL[87]. **Lipoproteinas de baixa densidade (LDL) elevado:** valores maiores do que 150mg/dl[87]. **Hipertrigliceridemia:** concentração de triglicerídeos maior do que 150mg/dl[87]. Em todos os testes sanguíneos, sangue foi coletado após 08-12 horas de jejum. **Obesidade e sobrepeso:** a circunferência abdominal foi medida com uma fita métrica estando o indivíduo em ortostase com a fita métrica passando entre a crista ilíaca e a ultima costela[88]. Foi considerado circunferência abdominal aumentada quando esta foi maior que 102cm. A obesidade foi mensurada pelo IMC calculado dividindo o peso do paciente pelo quadrado da altura. Foram considerados valores abaixo do normal os valores abaixo de 18.5 Kg/m^2, normal entre 18.5 Kg/m^2 até 24.9 Kg/m^2, sobre peso 25.0 Kg/m^2 até 29.9 Kg/m^2 e obeso acima de 30Kg/m^2 [26]. **Síndrome metabólica:**

Presença de 3 dos 5 critérios: HAS; gordura abdominal aumentada (circunferência adominal maior que 102cm em homens); nível sérico de HDL colesterol menor que 40mg/dL; glicemia sérica em jejum acima de 100mg/dL; triglicerídeo acima de 150mg/dL[88].

ASPECTOS ÉTICOS: O estudo foi aprovado pelo Comitê de Ética e Pesquisa do Complexo Hospitalar Universitário Professor Edgard Santos e todos os pacientes assinaram o termo de consentimento.

ANÁLISE ESTATÍSTICA: As variáveis contínuas foram resumidas através de média e desvio padrão enquanto as variáveis categóricas foram apresentadas sob forma de frequências simples e relativas. Os pacientes foram estratificados em dois grupos: Com DE e Sem DE. O teste t de Student foi utilizado para comparar médias e os testes de X^2 ou Fisher, conforme indicado, utilizados para comparar proporções entre os grupos. A técnica de correlação de *Spearman* foi utilizada para avaliar a correlação entre DE (IIEF-5) com o grau de comprometimento neurológico (EDSS) e obesidade (IMC). A regressão logística binária foi utilizada para identificar preditores de DE em pacientes portadores assintomáticos de HTLV-1. Os resultados foram considerados estatisticamente significantes quando o valor de P foi < 0,05. A analise estatística foi feita com o SPSS versão 17.0.

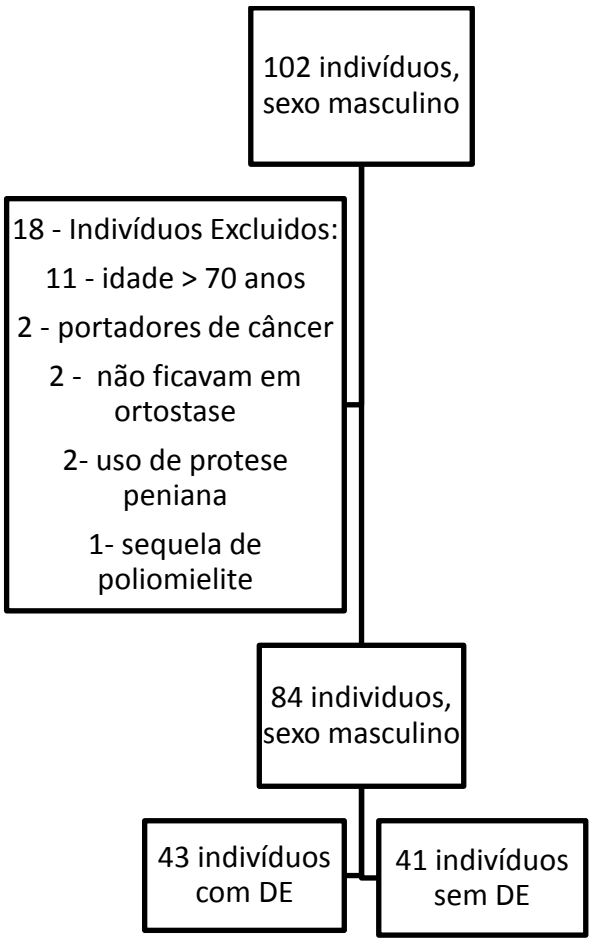
Cálculo amostral

O tamanho da amostra do estudo foi baseada de acordo com a proporção de obesos na Bahia, segundo dados do Ministério da Saúde do Brasil, que é de 17,4% e a estimativa de indivíduos infectados pelo HTLV-1 com DE foi de 40%[89]. Baseado nesses dados o tamanho mínimo da amostra deve ser de 73 pacientes se a confiança for de 95% e de 51 pacientes se a confiança for de 90%, estabelecida por Lwanga and Lemeshow[90].

RESULTADOS

Um total de 102 pacientes do sexo masculino foram avaliados, 18 foram excluídos do estudo conforme apresentado na figura 1.

Figura 1. Organograma dos indivíduos selecionados de acordo com os critérios do estudo.



A média de idade dos 84 pacientes avaliados foi de 54 ± 10,5 (variando de 18 até 69 anos). A prevalência de DE na população estudada foi de 51,2%. Os pacientes com DE tinham maior média de idade que os pacientes sem DE (58 ± 8,5 contra 49 ± 10,5; P=0,002). Os indivíduos infectados pelo HTLV-1 foram estratificados em dois grupos um com DE e outro sem DE e esses grupos foram comparados avaliando idade, IMC, circunferência abdominal elevada, na tabela 1 já os sintomas neurológicos associados ao HTLV-1 e os fatores de risco para arteriosclerose é mostrado na tabela 2.

Tabela 1: Aspectos demográficos de 84 indivíduos infectados pelo HTLV-1, estratificados para a presença de disfunção erétil.

Variáveis	Disfunção erétil		P
	Com DE (n = 43) N (%)	Sem DE (n = 41) N (%)	
Idade (anos)			
<60	23 (53,5)	35 (85,4)	**0,002**
≥60	20 (46,5)	6 (14,6)	
C A	15 (34,9%)	11 (26,8%)	0,57
IMC			
Baixo peso	2 (4,7%)	0 (0,0%)	
Normal	18 (41,9%)	16 (39%)	
Sobrepeso	14 (32,6%)	14 (34,1%)	0,51
Obesidade	9 (20,9%)	11 (26,8%)	

Legenda: DE = disfunção erétil; CA elevada circunferência abdominal elevada; IMC: índice de massa corpórea

Tabela 2: Sintomas neurológicos e fatores de risco para arteriosclerose de 84 indivíduos infectados pelo HTLV-1, estratificados para a presença de disfunção erétil.

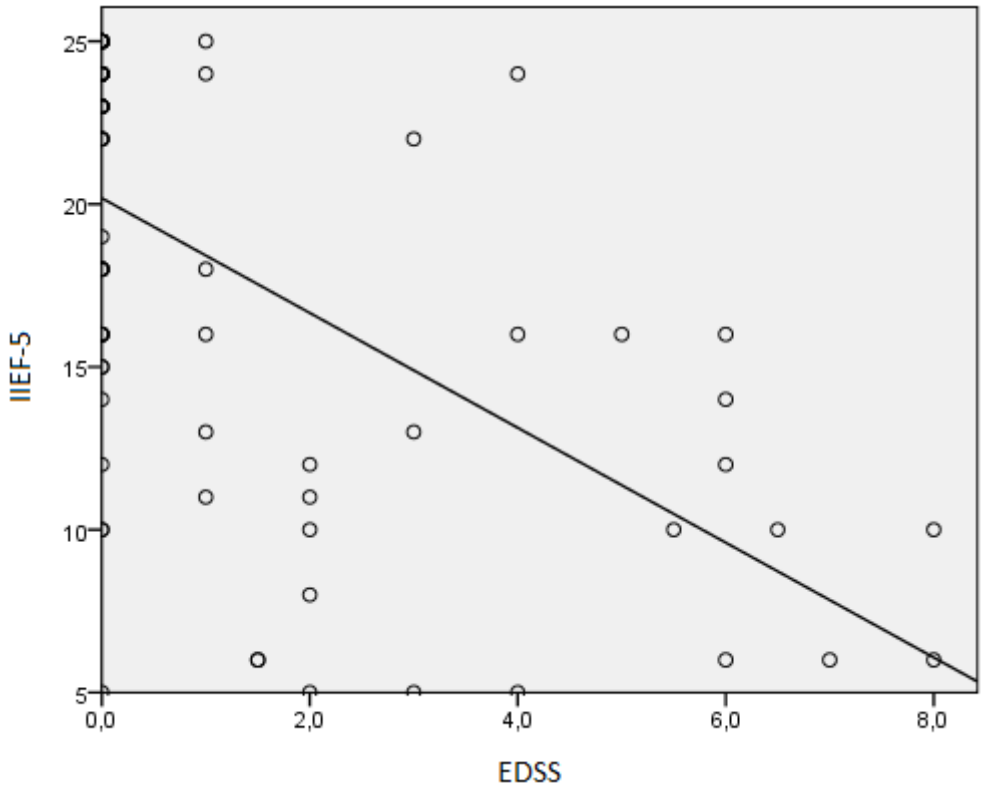
Variáveis	Disfunção erétil		P
	Com DE (n = 43) N (%)	Sem DE (n = 41) N (%)	
Sintomas neurológicos			
Assintomático	18 (41,9)	37 (90,2)	
Provável HAM/TSP	11 (25,6)	2 (4,9)	**<0,001**
HAM/TSP	14 (32,6)	2 (4,9)	
FR arterioesclerose			
DM	8 (18,6)	1 (2,4)	**0,03**
HAS	16 (37,2)	8 (19,5)	0,12
LDL elevado	10 (23,3)	8 (19,5)	0,87
HDL baixo	17 (39,5)	12 (29,3)	0,44
Triglicerídeos elevados	15(34,9)	10 (24,4)	0,41
Síndrome metabólica	11 (25,5)	4 (9,7)	0,08

Legenda: DE = disfunção erétil; HAM/TSP = paraparesia espástica tropical linfoma/leucemia de células T do adulto; FE = fatores de risco; DM = diabetes mellitus; HAS = hipertensão arterial sistêmica; LDL = lipoproteínas de baixa densidade; HDL = lipoproteínas de alta densidade.

Dos fatores de risco para a arteriosclerose apenas o DM teve relação estatisticamente significativa com a DE (P=0,030). Avaliando a associação entre DE e as manifestações clínicas do HTLV-1, houve relação estatisticamente significativa com provável HAM/TSP e HAM/TSP (P<0,001). Também houve associação de DE com a idade acima de 60 anos (P=0,002).

Associação entre a DE e a gravidade das lesões neurológicas do HTLV-1 é demonstrada na figura 2.

Figura 2: Associação entre a gravidade da disfunção neurológica medida pelo EDSS e o grau de disfunção erétil medido pelo IIEF-5.

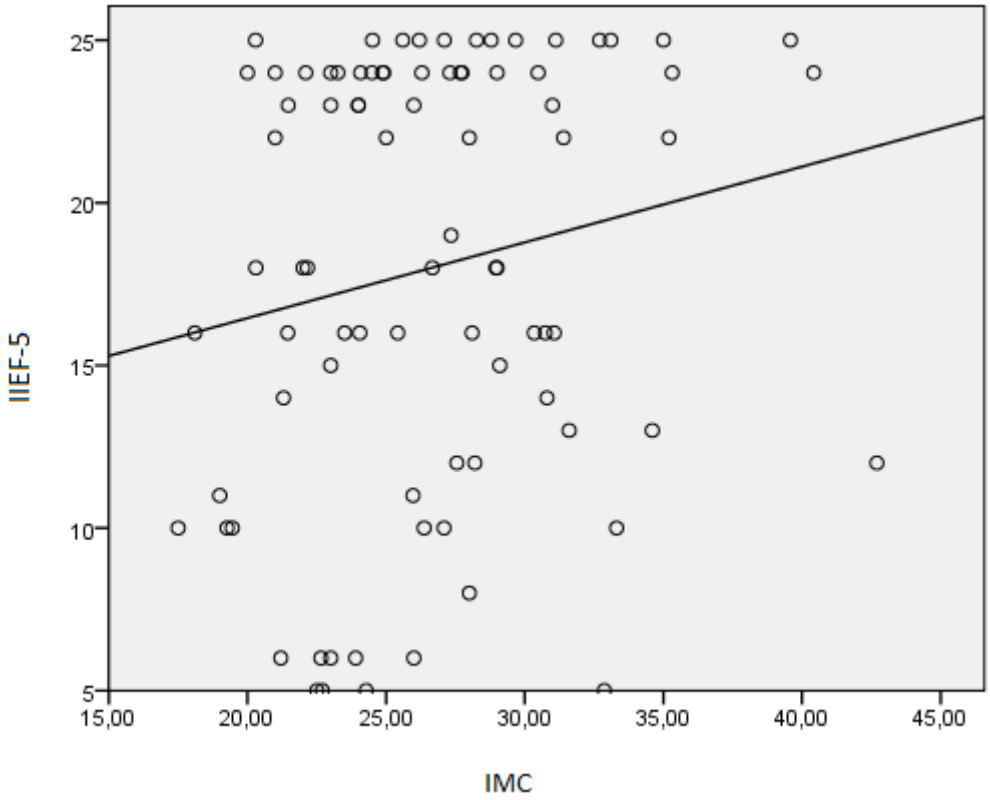


Legenda: IIEF-5: *International Index of Erectile Dysfunction;* EDSS: *Expanded Disability Status Scale* (P<0,001) (R=0,332)

Houve associação significativa entre o grau de disfunção neurológica medido pelo EDSS com o grau de DE medido pelo IIEF-5 (P<0,001) (Figura 2). Quanto maior foi o EDSS mais grave foi a DE e mais baixo o valor de IIEF-5.

A associação entre DE e o IMC está representada na figura 3.

Figura 3: Associação entre IMC e IIEF-5.



Legenda: IIEF-5: *International Index of Erectile Dysfunction;* IMC: Índice de Massa Corpórea (P=0,10) (R=0,031)

Não foi encontrada associação entre o grau de função erétil medido pelo IIEF-5 com o IMC (P=0.10) (Figura 3).

Fazendo uma regressão logística univariada analisando DE com os dados demográficos e os fatores de risco para arteriosclerose foi encontrada uma odds ratio de 5,0 para idade acima de 60 anos, 9,1 para DM, 2,4 para HAS, 3,1 para síndrome metabólica e 12,8 para os pacientes com sintomas neurológicos de HTLV-1 (tabela 3). Sendo que foram considerados os pacientes sintomáticos para HTVL-1 os pacientes com provável HAM/TSP e com HAM/TSP.

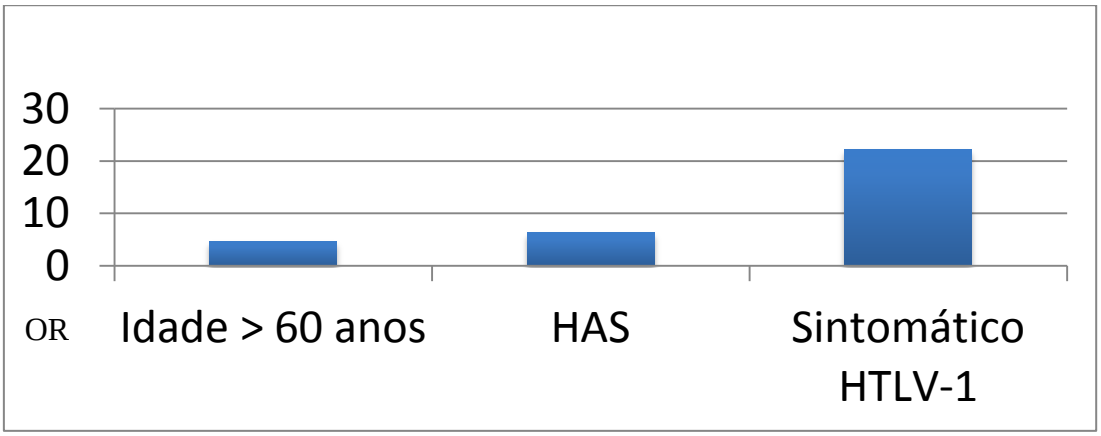
Tabela 3. Regressão logística univariada avaliando a associação de disfunção erétil e fatores de risco para arteriosclerose em 84 indivíduos infectados pelo HTLV-1 estratificados com e sem DE.

Variáveis independentes para DE	OR	95% I.C.		P
		Menor	Maior	
Idade > 60 years	5.072	1.769	14.541	0.003
DM	9.143	1.089	76.765	0.042
HAS	2.444	0.909	6.575	0.077
Síndrome metabólica	3.180	0.922	10.969	0.067
Sintomático HTLV-1	12.847	3.884	42.499	≤0.001

Legenda: DE = disfunção erétil; OR= Razão de chance; DM = diabetes mellitus; HAS= hipertenção arterial sistêmica.

Fazendo uma regressão logística multivariada foi encontrado um odds ratio de 4,6 para idade acima de 60 anos, de 6,3 para HAS, de 22,1 nos sintomáticos para HTLV-1 (figura 4).

Figura 4. Regressão logística multivariada avaliando a associação de disfunção erétil e fatores de risco para arteriosclerose em 84 indivíduos infectados pelo HTLV-1 estratificados com e sem DE.



Legenda: OR = Odds Ratio; HAS = hipertensão arterial sistêmica; Sintomático HTLV-1 = indivíduos com provável HAM/TSP e com HAM/TSP.

Devido a forte associação entre DE e as manifestações clínicas do HTLV-1, foi feita a avaliação da associação de DE com os fatores de risco para disfunção erétil nos 55 indivíduos portadores de HTLV-1 (Tabela 4).

Tabela 4: Aspectos demográficos e clínicos de 55 portadores assintomáticos de HTLV-1, estratificados para a presença de disfunção erétil.

Variáveis	**Disfunção erétil**		**P**
	Com DE (n = 18) N (%)	**Sem DE (n = 37) N (%)**	
Idade (anos)			
<60	10 (55,6)	31 (83,8)	0,024
≥60	8 (44,4)	6 (16,2)	
FR arterioesclerose			
DM	3 (16,7)	0 (0,0)	0,010
HAS	11 (61,1)	8 (21,6)	0,004
LDL elevado	3 (16,7,3)	7 (18,9)	0,839
HDL baixo	6 (33,3)	12 (32,4)	0,947
Triglicerídeos elevados	8(44,4)	10 (27,0)	0,196
Síndrome metabólica	5 (27,8)	4 (10,8)	0,110
CA elevada	5 (27,8)	10 (27,0)	0,953
IMC			
Normal	6 (33,3)	13 (35,1)	
Sobrepeso	8 (44,4)	14 (37,8)	
Obesidade	4 (22,2)	10 (27,0)	0,881

Legenda: DE = disfunção erétil; DM = diabetes mellitus; HAS = hipertensão arterial sistêmica; LDL = lipoproteínas de baixa densidade; HDL = lipoproteínas de alta

densidade; CA elevada = circunferência abdominal elevada; IMC: índice de massa corpórea

A média de idade dos 55 pacientes avaliados foi de 53 ± 9,3 (variando de 26 até 69 anos). Houve relação estatisticamente significante com DE nos indivíduos com mais de 60 anos (P=0,024), com DM (P=0,010) e HAS (P=0,004). A regressão logística univariada apresentou uma odds ratio de 8,5 para HAS. A DM não pode ser avaliada pois todos os diabéticos do estudo tinham DE e a regressão logística não consegui calcular o odds ratio nessa situação.

DISCUSSÃO

Estudos na literatura mostram que a DE está relacionada com o HTLV-1 e que existe uma clara relação da DE e a gravidade da DE com o grau de lesão neurológica[3, 4]. Entre tanto, esses estudos também demonstram que existem indivíduos portadores do HTLV-1 que desenvolvem DE[91]. DE, na população geral, pode ter origem vascular[25], endócrina[50], neurológica[77] e psicogênica[74]. Sendo que a causa vascular é a mais importante e está associada a lesões endoteliais secundárias a arteriosclerose[13].

O Objetivo do presente estudo foi correlacionar a disfunção erétil em indivíduos infectados pelo HTLV-1 com fatores de risco para arteriosclerose como a obesidade, dislipidemia, hipertensão, diabetes, síndrome metabólica e comprometimento neurológico do HTLV-1. No estudo foi demonstrado que os fatores de risco para a arteriosclerose podem contribuir para a DE em indivíduos infectados pelo HTLV-1 porém a DE apresentou maior associação com o grau de disfunção neurológica dos indivíduos.

Ao contrário do que acontece com a população geral em que os fatores de risco para a arteriosclerose apresentam uma grande influência na DE[11, 66], no presente estudo apresentado apenas o DM teve correlação com DE. Fazendo a regressão logística univariada foi evidenciado que o DM, HAS e o grau de desenvolvimento neurológico tinham forte influência na DE desses indivíduos. Porém ao fazer a regressão multivariada foi evidenciado que o grau de lesão neurológica secundário ao HTLV-1 foi o principal fator relacionado com a DE. Os fatores de risco para arteriosclerose tiveram uma associação com DE especialmente a HAS porém essa associação foi mais fraca que a associação da DE com o grau de lesão neurológica secundário ao HTLV-1. Outros fatores de risco para a arteriosclerose como obesidade[66], dislipidemia[33], síndrome metabólica[92] e circunferência abdominal[57] aumentada não tiveram uma forte relação com a DE. A idade acima de 60 anos, como é demonstrado em estudos avaliando DE na população geral[66], apresentou uma associação com DE. Ocorreu, como nos estudos anteriores avaliando DE na população infectada pelo HTLV-1, uma forte associação da DE com o grau de manifestação neurológica do HTLV-1 tanto nos indivíduos com HAM/TSP como nos com provável HAM/TSP[3]. Este fato evidencia que a DE, nessa população, está mais relacionada com os fatores de origem neurológica causados pelo HTLV-1 do que com os fatores de origem vascular causada pela arteriosclerose.

Esta descrito na literatura que a DE pode se apresentar em indivíduos previamente assintomáticos como sua primeira manifestação clínica[5]. Em indivíduos portadores de HTLV-1 era esperado que houvesse uma associação maior da DE com os fatores de risco para a arteriosclerose, já que essa população não apresenta nenhum comprometimento neurológico. Porém essa associação não foi encontrada no estudo. Fatores de risco para arteriosclerose como a obesidade, circunferência abdominal aumentada[57, 93], síndrome metabólica[92] e dislipidemia[92] não apresentaram associação com DE. Nos portadores de HTLV-1 houve associação da DE com a idade acima de 60 anos e dos fatores de risco para a arteriosclerose houve associação com DM e HAS. Fazendo a regressão logística univariada a HAS apresentou uma forte associação com a DE. A DM não pode ser avaliação pela regressão logística pois todos os pacientes com DM tinham DE. Esses dados apontam que a DE nesse grupo específico pode sinalizar uma manifestação precoce de lesão neurológica.

A DE em indivíduos infectados pelo HTLV-1 ainda precisa ser melhor estudada é necessário que sejam feitos novas pesquisas para que sejam descobertas as suas causas.

A associação de DE com o grau de disfunção neurológica já foi bem descrito e documentado na literatura[3, 4]. Porém deveriam ser realizados estudos mais específicos e mais objetivos como a utilização da eletroneuromiografia[79] para demonstrar mais precisamente que a lesão neurológica e sua relação com a DE são secundários ao HTLV-1 e afastar outras causas de DE relacionadas a lesões neurológicas secundárias a outras patologias[79]. Existe a necessidade de que sejam avaliadas, em indivíduos infectados pelo HTLV-1, se as causas de DE na população geral como a arteriosclerose[25], disfunção hormonal[94] e patologias psicogênicas[74] estão associadas com a DE nesse grupo específico de indivíduos. O estudo realizado avaliou a associação dos fatores de risco para arteriosclerose, uma das principais causas de DE na população geral[25], com a DE em indivíduos infectados pelo HTLV-1 porém não encontrou uma forte associação desses fatores com a DE. É necessários que sejam feitos estudos mais específicos para avaliar as artérias penianas desses indivíduos como estudos utilizando ultrassonografia com Doppler[58] para que seja feita uma avaliação mais objetiva do fluxo sanguíneo, da perviedade dessas artérias identificando a real influência da arteriosclerose na DE desses indivíduos. Devem ser feitos também estudos avaliando a dosagem sérica de hormônios como a TT[76] e avaliar se existe uma associação dos níveis de TT baixos com DE nesses indivíduos. Também devem ser feitos estudos avaliando a influência de patologias psicogênicas como a ansiedade a depressão e a sua associação com DE[74] nesses indivíduos já que o HTLV-1, especialmente na forma HAM/TSP, pode manifestar sintomas graves, debilitantes, incapacitantes, dores crônicas que podem levar ao desenvolvimento de distúrbios psicogênicos nos indivíduos.

O estudo das causas de DE em indivíduos infectados pelo HTLV-1 vai além de uma simples investigação urológica de disfunção erétil pois servi como um rastreamento e um acompanhamento multiprofissional para varias patologias que estão associadas a DE. No presente estudo investigando os fatores de risco para a arteriosclerose nos indivíduos foi possível fazer uma avaliação clínica ampla um melhor controle, diagnóstico e tratamento de patologias como DM, HAS, obesidade, síndrome metabólica, dislipidemia, o encaminhamento dos indivíduos para o tratamento especializado quando necessário. Ocorreram alguns ajustes de medicação, alguns diagnósticos de patologias que ainda não haviam sido descobertas. Foram identificados indivíduos com obesidade, indivíduos com IMC abaixo do normal e eles foram encaminhados para fazer uma avaliação nutricional e endócrina. Nos indivíduos infectados pelo HTLV-1 nunca havia sido feito um estudo que avaliasse o IMC e a circunferência abdominal dessa população. Esse fato também serviu para alertar sobre os problemas relacionados com a obesidade e o baixo peso nesses indivíduos. No estudo realizado os 2 pacientes com IMC abaixo do normal eram portadores de HAM/TSP. Indicando a necessidade de realizar mais estudos avaliando o IMC dos indivíduos e associando a outros fatores relacionados a infecção pelo HTLV-1 como o grau de disfunção neurológica, citocinas e carga proviral. A avaliação do IMC é uma avaliação relativamente simples de relativo baixo custo, fácil execução, permite que sejam tomadas varias medidas com passar do tempo o que torna viável a realização de estudos nessa área. Vale lembrar que os indivíduos infectados pelo HTLV-1 provável HAM/TSP e HAM/TSP tende a ser mais sedentários devido ao quadro clínico da doença que em alguns casos impede ou dificulta a movimentação.

Apesar do estudo não mostrar uma forte associação da DE com os fatores de risco para arteriosclerose em indivíduos infectados pelo HTLV-1, o fato de um indivíduo apresentar DE serve de alerta para uma serie de patologias relacionadas com a DE e que muitas vezes não são diagnosticadas. Além da contribuição científica e urológica deste

estudo, houve uma contribuição na avaliação clínica global dos indivíduos da coorte e serve de alerta que a obesidade também está presente e precisa ser melhor avaliada nessa população.

PERSPECTIVAS DE ESTUDO

1- Avaliação da artérias penianas utilizando ultrassonografia com Doppler para a avaliar o fluxo sanguíneo dessas artérias em indivíduos infectados pelo HTLV-1.
2- Avaliação com eletroneuromiografia da inervação peniana relacionada com a ereção em indivíduos infectados pelo HTLV-1.
3- Avaliação de fatores endócrinos relacionados com a ereção em indivíduos infectados pelo HTLV-1.
4- Avaliação de fatores psicogênicos relacionados com a disfunção erétil em indivíduos infectados pelo HTLV-1.

CONCLUSÕES

1- Dos fatores de risco para a arteriosclerose avaliados apenas a DM e HAS apresentaram associação com a DE em indivíduos infectados pelo HTLV-1.
2- A principal associação de DE em indivíduos infectados pelo HTLV-1 são as manifestações neurológicas dessa doença.

Evaluation of risk factors for atherosclerosis in HTLV-1 infected patients with Erectile Dysfunction.

Erectile dysfunction in individuals infected with HTLV-1 is strongly associated with neurological dysfunctions caused by this disease. However, the main cause of erectile dysfunction in the general population is arteriosclerosis which leads to a decrease in blood flow to the corpus cavernosum. The aim of this study was to evaluate whether there is an association between the risk factors for atherosclerosis with erectile dysfunction in individuals infected with HTLV-1. Methods: Cross-sectional study with males infected with HTLV-1 between 18 and 70 years with no history of cancer, without the use of penile prosthesis and no motor deficit caused by another condition. Participants of the study subjects were classified into two groups: one group with ED and a group without ED. These groups were compared and evaluated the relationship between obesity, increased waist circumference, dyslipidemia, metabolic syndrome, diabetes mellitus and arterial hypertension. Results: Of the 84 selected individuals 43 had erectile dysfunction and 41 did not. There was a relationship of erectile dysfunction with diabetes mellitus (P = 0.03), age over 60 years (P = 0.002) and the degree of neurological dysfunction (P <0.001). Odds ratio 22,1 for symptomic HTLV-1, 6,2 for HBP and 43 for age more than 60 years. Among the risk factors for atherosclerosis evaluated in HTLV-1 carriers was association with ED with age over 60 years (P = 0.024) with diabetes mellitus (P = 0.01) and hypertension (P = 0.004). Odds ratio 22,1 for symptomic HTLV-1, 6,2 for HBP and 43 for age more than 60 years. Conclusion: Neurological impairment is a major cause of erectile dysfunction in individuals infected with HTLV-1 and risk factors for arteriosclerosis did not have strong relationship with erectile dysfunction in this population.

Keywords: 1. erectile dysfunction; 2- Human T-lymphotropic virus 1; 3- arteriosclerosis

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ARTIGO

"Risk factors for atherosclerosis in HTLV-1 infected patients with erectile dysfunction". Urology (submetido, vide Normas de Publicação no Anexo e carta ao Editor, no Anexo 3 e 4).

Cassius J.V. Oliveira[a,b], José A. Neto[a,b], Rosana C.P.Andrade[b,c], Paulo N Rocha [d], Edgar M. Carvalho[b,d]

[a] Postgraduate Program in Health Sciences, Federal University of Bahia School of Medicine, Salvador, Brazil.

[b] Immunology Service, Complexo Hospitalar Professor Edgard Santos, Universidade Federal da Bahia (UFBA) Salvador, Bahia, Brazil.

[c] Physiotherapy department, Complexo Hospitalar Professor Edgard Santos, Universidade Federal da Bahia (UFBA) Salvador, Bahia, Brazil.

[d] Department of Medicine and Diagnostic Support, Medical School of Bahia of the Federal University of Bahia

Short title: Traditional risk factors for ED in HTLV-1 patients

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[*]Corresponding author: Edgar M. Carvalho, MD/PhD, Serviço de Imunologia, Hospital Universitário Professor Edgard Santos, Universidade Federal da Bahia-UFBA, 5º andar, Rua João das Botas, s/n, Canela, 40110060, Salvador, Bahia, Brazil. Phone: 55 71 3245-5493, Fax: 55 71 3245-7110, e-mail: edgar@ufba.br

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ABSTRACT

Objective: Evaluate whether there is an association between the risk factors for atherosclerosis with ED in individuals infected with HTLV-1. **Methods:** Cross-sectional study with males infected with HTLV-1 between 18 and 70 years with no history of cancer, without the use of penile prosthesis and no motor deficit caused by another condition. Participants stratified into two groups according to the presence or absence of ED. These groups were compared in regards to obesity, increased waist circumference, dyslipidemia, metabolic syndrome, diabetes mellitus (DM) and high blood pressure (HBP). **Results:** Of the 84 selected individuals, 43 had ED and 41 did not. In univariate analysis, there was a significant association between ED and DM (P = 0.03), age > 60 years (P = 0.002) and the degree of neurological dysfunction (P <0.001). In a multivariate analysis, symptomatic HTLV-1 infection showed the greatest association with ED (adjusted OR 22.1; 95% CI 5.3-92.3), followed by HBP (adjusted OR 6.3; 95 CI 1.4-30.5) and age over 60 years (adjusted OR 4.6; 95% CI 1.3-17.3). In the subgroup of patients with asymptomatic HTLV-1 infection, ED was associated with age > 60 years (P = 0.024), DM (P = 0.01) and HBP (P = 0.004). **Conclusion:** Neurological impairment is the major cause of ED in individuals infected with HTLV-1. However, traditional risk factors for atherosclerosis remain associated with ED in this population, especially among the subgroup of individuals with asymptomatic HTLV-1 infection.

INTRODUCTION

The human T cell lymphotropic virus type 1 (HTLV-1) was identified in 1980[1], and is the etiological agent of HTLV-1 associated myelopathy, also known as tropical spastic paraparesis (HAM/TSP), and of the adult T cell leukemia/lymphoma[2]. It is estimated that about 5 to 10 million people are infected by HTLV-1 worldwide mainly on southwestern Japan, the Caribbean, Africa and South and Central and America[3].

Only a minority of infected patients develop HAM/TSP that is caused by a progressive inflammatory response and demyelination of the spinal cord[4, 5]. The neurological injuries also lead to other symptoms, such as decreased strength, pain and spasticity in the lower limbs and sphincter disorders[6, 7]. Urinary symptoms, mainly of overactive bladder (OAB), occur in up to 20% of the HTLV-1 infected subjects who do not fulfill the diagnosis of HAM/TSP[3] is observed in up to 50% of infected individuals. In a study evaluating the frequency of erectile dysfunction (ED) in this population, it was shown that ED was present in 35% of HTLV-1 carriers, in 79% of patients with probable HAM/TSP and in 93.7% of patients with HAM/TSP[8].

While there is a clear relationship between ED and the degree of neurological impairment in HTLV-1, ED may also occur in HTLV-1 infected subjects without neurologic manifestations. In the general population, age, atherosclerosis and diabetes mellitus (DM) are the most important risk factors for ED. Atherosclerosis leads to occlusive vessel phenomena that impair adequate blood flow to the penile arteries and micro vessels of the cavernous bodies, resulting in ED[9-11]. Studies evaluating the intensity of the blood flow in the penile arteries by Doppler ultrasonography demonstrate that atherosclerosis of these arteries correlates with decreased blood flow and ED[12, 13]. Atherosclerosis has been recognized as an inflammatory illness and HTLV-1 is associated with an exaggerated production of pro-inflammatory cytokines[14, 15].

As ED is documented in individuals infected with HTLV-1 without evidence of neurological damage and atherosclerosis is a major cause of ED in the general population, we evaluated if there was an association between ED and traditional risk factors for atherosclerosis, such as DM, high blood pressure (HBP), dyslipidemia, metabolic syndrome and obesity in individuals infected with HTLV-1.

MATERIALS AND METHODS

Design and population

This is a cross sectional study conducted in the multidisciplinary HTLV-1 clinic of the University Hospital of the Federal University of Bahia. Patients were enrolled between January 2013 and June 2015. Inclusion criterion was a positive ELISA test for HTLV-1 confirmed by Western blot. Exclusion criteria were age < 18 or > 70 years, history of cancer, use of penile prosthesis, a motor deficit due to other neurologic disorders.

Definition of Variables

Evaluation of neurologic impairment and clinical forms of HTLV-1 infection: the degree of neurological impairment of the participants was evaluated by the Osame's motor disability scale (ODMS) and the expanded disability status scale (EDSS)[16]. Individuals with Osame = 0 and EDSS = 0 were considered HTLV-1 carriers, or asymptomatic from a neurologic standpoint. Probable HAM/TSP was defined according to Castro-Costa classification[17]. These patients had ODMS = 0 and EDSS > 0 and < 3. Patients with HAM/TSP had ODMS ≥ 1 and EDSS ≥ 3 had HAM/TSP[17]. Patients with

probable HAM/TSP or HAM/TSP were considered to have symptomatic HTLV-1 infection.

Evaluation of erectile function: The international index of erectile function (IIEF-5) was used to evaluate the degree of ED. It is a self-applied questionnaire with results ranging from 5 to 25. Individuals with IIEF-5 greater than 21 are considered to have normal erectile function. Individuals scoring 5 to 7 points are have severe ED, 8 to 11 = moderate, 11-16 = moderate light and 17-21 light ED[18].

Definition of atherosclerosis risk factors: DM[19] and HBP[20] were defined by clinical history or documentation of fasting blood sugar > 125 mg/dl or higher than 175mg/dl after a meal and blood pressure higher than 140 / 85 mmHg. Hypercholesterolemia was defined as total cholesterol levels greater than 200 mg/dl[21, 22], low high density lipoprotein (HDL) cholesterol when levels were lower than 40 mg/dl[21, 22] and high low density lipoprotein (LDL) when levels were higher than 150 mg/dl[21, 22]. Hypertriglyceridemia was defined as triglycerides higher than 150 mg/dl[21, 22] in blood collected after 10-12 hours of fasting. Overweight and obesity were determined by the body mass index (BMI) and waist circumference[22, 23]. The waist circumference was measured between the iliac crest and the last rib with the individual in the standing position. Increased waist circumference was defined as greater than 102 cm. The BMI was calculated by dividing the patient's weight by the square of height. Values ranging from 18.5 kg/m2 to 24.9 kg/m2 were considered normal, 25.0 kg/m2 to 29.9 kg/m2 = overweight, and above 30 kg/m2 = obesity[22]. Metabolic syndrome was defined by the presence of 3 out of the following 5 criteria: HBP; increased abdominal fat (abdominal circumference greater than 102 cm in men); serum level of HDL cholesterol lower than 40 mg/dl; serum fasting glucose above 100 mg/dl; triglycerides above 150mg/dl.

Ethical issues

This study was approved by the Research Ethics Committee of the Federal University of Bahia, University Hospital, and all patients provided a written informed consent.

Statistical analysis

Continuous variables were expressed as mean and standard deviation while categorical variables were presented as absolute and relative frequencies. Patients were stratified into two groups according to the presence or absence of ED. The Student's t test was used to compare means and X^2 or Fisher's exact test, as indicated, were used to compare proportions between groups. The Spearman's correlation technique was used to evaluate the correlation between ED and the degree of neurological impairment (EDSS) and between ED and obesity (BMI). A binary logistic regression analysis was conducted to identify predictors of ED in symptomatic and asymptomatic patients with HTLV-1. The results were considered statistically significant when $P < 0.05$ in final analyses. All statistical analyses were performed using SPSS version 17.

RESULTS

A total of 102 male patients were evaluated and 18 were excluded because they were older than 70 years, 11 due to cancer, 2 failed to stay standing, 2 had penile prosthesis and 1 patient had neurologic impairment due to poliomyelitis. The mean age ± standard deviation of the 84 participants was 54 ± 10.5 years, and the overall frequency of ED was 51.2%. Table 1 shows the demographic, clinic and laboratory data of 84 HTLV-1 infected subjects stratified by the presence or absence of ED. ED was significantly associated with age > 60 years, degree of neurologic involvement and DM but not with HBP, high LDL, low HDL, high triglycerides, metabolic syndrome or BMI.

To further explore the risk factors for ED among HTLV-1 infected subjects, we conducted univariate and multivariate logistic regression analyses. On univariate

analyses (Table 2),symptomatic HTLV-1 infection showed the greatest association with ED, followed by DM and age > 60 years; metabolic syndrome and HBP showed a trend but were not statistically significantly associated with ED. In the multivariate analysis, symptomatic HTLV-1 infection remained the most important risk factor for ED (adjusted OR 22.1; 95% CI 5.3-92.3), followed distantly by HBP (adjusted OR 6.3; 95 CI 1.4-30.5) and age > 60 years (adjusted OR 4.6; 95% CI 1.3-17.3). (Figure-1)

Because of the strong association between ED and neurologic manifestations of HTLV-1, we decided to evaluate if there was an association of risk factors for atherosclerosis with ED in the 55 subjects who had asymptomatic HTLV-1 infection (Table 3). The mean age of these 55 subjects was 53.5 ± 9.3 (range, 26 to 69 years). There was an association of ED with age > 60 years (P = 0.02), DM (P = 0.01) and HBP (P = 0.004). However there was no association of ED with dyslipidemia, metabolic syndrome or BMI

DISCUSSION

HAM/TSP is a severe disease caused by HTLV-1 but it only occurs in a small percentage of infected individuals[24]. However, evidence has been accumulated in the last 10 years that a large percentage of HTLV-1 infected individuals have other clinical manifestations[25]. Previous studies have shown a strong association between ED and HTLV-1 infection. Moreover a large percentage of HTLV-1 infected individuals have severe or moderate ED[8].

While it is clear that the prevalence of ED increases with the degree of neurologic disability, there is a large number of HTLV-1 infected subjects who do not have neurologic manifestations and have ED[4]. However ED is a frequent complaint in the general population in whom the main cause of ED is atherosclerosis and its risk factors, such as dyslipidemia, increase in abdominal circumference, obesity, HBP and DM[21]. Herein, we showed that although atherosclerosis may contribute to the ED observed in HTLV-1, the main cause of ED in these individuals is neurologic disease.

In a Brazilian study with individuals without HTLV-1, it was observed that 52% of men 40 to 70 years old had some degree of ED[26]. The pathophysiology of ED can be vascular, neurogenic, psychogenic and endocrine[27]. Erection is a vascular event and atherosclerosis is the main cause of ED[27]. The prevalence of ED increase with age and in subjects over 70 years old the prevalence of ED is up to 80%[28]. Atherosclerosis also increases with age and the risk factors for atherosclerosis as dyslipidemia, metabolic syndrome, obesity, diabetes and HBP are highly associated with ED[29, 30]. In the present study, when the whole sample of HTLV-1 infected subjects was evaluated regarding ED and risk factors for atherosclerosis, the only association with ED was DM but it only occurs in 10% of the studied patients. There was no association of ED with high LDL, low HDL, high triglycerides, abdominal circumference or obesity. In the multivariate logistic regression model, the association between DM and ED was lost. In this analysis, symptomatic HTLV-1 increased the odds of ED 22 times, while HBP and age > 60 years increased those odds by 6.3 and 4.6 times, respectively. This finding reinforces the findings of previous studies linking ED with the degree of neurological manifestations of HTLV-1[8].

It has been estimated that only 10-19% of ED is neurogenic[31]. However in HTLV-1 ED was strongly associated with the degree of neurologic disease[8]. As a large number of HTLV-1 infected subjects considered as HTLV-1 carriers also have ED, we investigated

if there was an association between risk factors for atherosclerosis in the HTLV-1 carriers. When this subgroup was evaluated, we found that age > 60 years, DM and HBP were associated with ED. However, there was no association between ED with dyslipidemia, metabolic syndrome and obesity.In a study comparing HTLV-1 carriers referred predominantly from blood bank with seronegative controls, the prevalence of ED was higher in subjects infected with HTLV-1[25]. The cause of ED in HTLV-1 carriers has not been completely understood, but it has been documented that ED can be the first sign of HAM/TSP[4]. Moreover there is an association between ED and HTLV-1 pro-viral load and a great association between ED and urinary manifestations in patients who do not fulfill the criteria for HAM/TSP[32]. It is known that only a small percentage of patients with overactive bladder the more common urinary manifestations in HTLV-1 develop HAM/TSP[3, 25]. Therefore it is also possible that neurologic damage in the spinal cord not sufficient to induce other neurologic manifestations may be the cause of ED in HTLV-1[33].

Conclusion

Individuals infected with HTLV-1 have a high prevalence of ED, which is mostly caused by neurological damage. However, traditional risk factors for atherosclerosis remain associated with ED in this population, especially among the subgroup of individuals with asymptomatic HTLV-1 infection.

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Figure Legends

Table 1. Demographic, clinic and laboratory data from 84 HTLV-1 infected subjects stratified by the presence or absence of ED.

Foot Note: Legend: ED = erectile dysfunction; HAM / TSP = HTLV-associated myelopathy / tropical spastic paraparesis; DM = diabetes mellitus; HBP = high blood pressure; LDL = low density lipoproteins; HDL = high density lipoproteins; BMI: body mass index.

Table 2. Risk factors for ED among 84 HTLV-1 infected subjects by univariate logistic regression.

Foot Note: ED = erectile dysfunction; OR = Odds Ratio; C.I. = confidence interval; DM = diabetes mellitus; HBP= high blood pressure

Table 3. Association between erectile dysfunction and risk factors for atherosclerosis in 55 HTLV-1 infected subjects without neurologic disease.

Foot Note: ED = erectile dysfunction; DM = diabetes; LDL = low density lipoproteins; HDL = high density lipoproteins; CA high = high waist circumference; BMI: body mass index

Figure 1. Risk factors for ED among 84 HTLV-1 infected subjects by multivariate logistic regression

Table 1

Variables	Erectile dysfunction		P
	Yes (n = 43) n (%)	No (n = 41) n (%)	
Age (years)			
< 60	23 (53.5)	35 (85.4)	0.003
≥ 60	20 (46.5)	6 (14.6)	
Clinic forms of HTLV-1 infection			
Asymptomatic	18 (41.9)	37 (90.2)	
Probable HAM/TSP	11 (25.6)	2 (4.9)	<0.001
HAM/TSP	14 (32.6)	2 (4.9)	
Risk factors for atherosclerosis			
DM	8 (18.6)	1 (2.4)	0.03
HBP	16 (37.2)	8 (19.5)	0.12
High LDL	10 (23.3)	8 (19.5)	0.87
Low HDL	17 (39.5)	12 (29.3)	0.44
High triglycerides	15 (34.9)	10 (24.4)	0.41
Metabolic syndrome	11 (25.5)	4 (9.7)	0.08
Abdominal circumference	15 (34.9)	11 (26.8)	0.57
BMI			
Low weight	2 (4.7)	0 (0.0)	
Normal	18 (41.9)	16 (39)	0.51
Overweight	14 (32.6)	14 (34.1)	
Obesity	9 (20.9)	11 (26.8)	

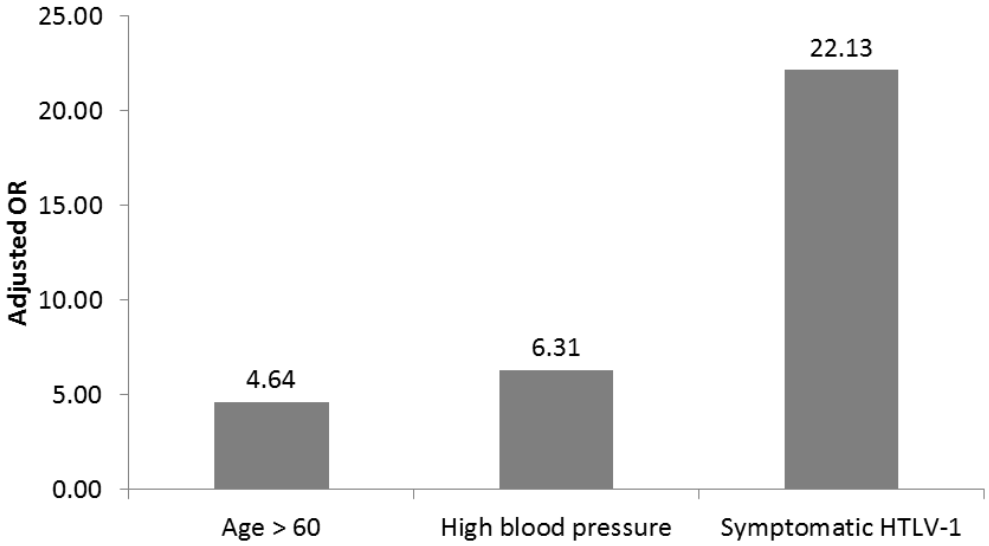
Table 2

Independent variables	OR	95% C.I.		P
		Lower	Upper	
Age > 60 years	5.072	1.769	14.541	0.003
DM	9.143	1.089	76.765	0.04
HBP	2.444	0.909	6.575	0.07
Metabolic syndrome	3.180	0.922	10.969	0.06
Symptomatic HTLV-1	12.847	3.884	42.499	≤0.001

Table 3

Variables	Erectile dysfunction		P
	Yes (n = 18) n (%)	No (n = 37) n (%)	
Age (years)			
<60	10(55.6)	31(83.8)	0.02
≥60	8 (44.4)	6(16.2)	
Risk factors for atherosclerosis			
DM	3 (16.7)	0 (0.0)	0.01
HBP	11 (61.1)	8 (21.6)	0.004
High LDL	3 (16.7.3)	7 (18.9)	0.83
Low HDL	6 (33.3)	12 (32.4)	0.94
High triglycerides	8 (44.4)	10 (27.0)	0.19
Metabolic syndrome	5 (27.8)	4 (10.8)	0.11
Abdominal circumference	5 (27.8)	10 (27.0)	0.95
BMI			
Normal	6 (33.3)	13 (35.1)	
Overweight	8 (44.4)	14 (37.8)	0.88
Obesity	4 (22.2)	10 (27.0)	

Figure 1


25.00
20.00
15.00
10.00
5.00
0.00
Adjusted OR
4.64
6.31
22.13
Age > 60
High blood pressure
Symptomatic HTLV-1

Considerações Finais

Existem alguns estudos que descrevem a associação da disfunção erétil com o grau de manifestação neurológica do HTLV-1. Porém não existem estudos associando a disfunção erétil com os outros fatores de risco para a disfunção erétil em indivíduos infectados pelo HTVL-1. Neste estudo, foi avaliado a associada da disfunção erétil com a arteriosclerose que é um dos principais fatores de risco para a disfunção erétil na população geral. Este estudo torna-se importante por relatar que a arteriosclerose não tem muita associação com a disfunção erétil e que o grau de manifestação neurológica tem maior relação com a disfunção erétil nessa população específica.

Anexos:

Anexo -1: IIEF-5: Índice Internacional de Função erétil:

1 – Com que freqüência você consegue uma ereção durante a atividade sexual?

0 = Não tentei ter relação sexual
1 = Quase nunca / Nunca
2 = Poucas vezes (muito menos que a metade das vezes)
3 = Algumas vezes (aproximadamente metade das vezes)
4 = Na maioria das vezes (muito mais que a metade das vezes)
5 = Quase sempre / Sempre

2 – Quando você tem ereções após estímulo sexual, com que freqüência suas ereções são suficientemente rígidas para penetração?

0 = Não tentei ter relação sexual
1 = Quase nunca / Nunca
2 = Poucas vezes (muito menos que a metade das vezes)
3 = Algumas vezes (aproximadamente metade das vezes)
4 = Na maioria das vezes (muito mais que a metade das vezes)
5 = Quase sempre / Sempre

3 – Quando você tentou ter uma relação sexual, com que freqüência você conseguiu penetrar sua companheira?

0 = Não tentei ter relação sexual
1 = Quase nunca / Nunca
2 = Poucas vezes (muito menos que a metade das vezes)
3 = Algumas vezes (aproximadamente metade das vezes)
4 = Na maioria das vezes (muito mais que a metade das vezes)
5 = Quase sempre / Sempre

4 – Durante a relação sexual, com que freqüência você consegue manter a ereção depois de ter penetrado sua companheira?

0 = Não tentei ter relação sexual
1 = Quase nunca / Nunca
2 = Poucas vezes (muito menos que a metade das vezes)
3 = Algumas vezes (aproximadamente metade das vezes)
4 = Na maioria das vezes (muito mais que a metade das vezes)
5 = Quase sempre / Sempre

5 – Durante a relação sexual, qual seu grau de dificuldade para manter a ereção até completar a relação sexual?

0 = Não tentei ter relação sexual
1 = Quase nunca / Nunca
2 = Poucas vezes (muito menos que a metade das vezes)
3 = Algumas vezes (aproximadamente metade das vezes)
4 = Na maioria das vezes (muito mais que a metade das vezes)
5 = Quase sempre / Sempre

Anexo -2: ESCALA EXPANDIDA DO ESTADO DE INCAPACIDADE - EDSS

ESCORE EDSS

Escore	Características	Escore Total
0	Exame neurológico normal (todos os SF grau 0; cerebral, grau 1 aceitável)	
1,0	Sem incapacidade (1 SF grau 1)	
1,5	Sem incapacidade (2 SF grau 1)	
2,0	Incapacidade mínima em 1 SF (1 SF grau 2, outros grau 0 ou 1)	
2,5	Incapacidade minima em 2 SF (2 SF grau 2, outros grau 0 ou 1)	
3,0	Incapacidade moderada em 1 SF (1 SF grau 3, outros grau 0 ou 1) ou incapacidade discreta em 3 ou 4 SF (3/4 SF grau 2, outros grau 0 ou 1). Deambulando plenamente.	
3,5	Deambulação plena, com incapacidade moderada em 1SF (1 SF grau 3) e 1 ou 2 SF grau 2; ou 2SF grau 3; ou 5 SF grau 2 (outros 0 ou 1)	
4,0	Deambulação plena, até 500 m sem ajuda ou descanso (1 SF grau 4, outros 0 ou 1)	
4,5	Deambulação plena, até 300 m sem ajuda ou descanso. Com alguma limitação da atividade ou requer assistência mínima (1 SF grau 4, outros 0 ou 1)	
5,0	Deambulação até 200 m sem ajuda ou descanso. Limitação nas atividades diárias (equivalentes são 1 SF grau 5, outros 0 ou 1; ou combinação de graus menores excedendo o escore 4.0)	
5,5	Deambulação até 100 m sem ajuda ou descanso. Incapacidade impedindo atividades plenas diárias (equivalentes são 1SF grau 5, outros 0 ou 1; ou combinações de graus menores excedendo o escore 4.0)	
6,0	Assistência intermitente ou com auxilio unilateral constante de bengala, muleta ou suporte (equivalentes são mais que 2 SF graus 3+)	
6,5	Assistência bilateral (equivalentes são mais que 2 SF graus 3+)	
7,0	Não anda 5 m mesmo com ajuda. Restrito a cadeira de rodas. Transfere da cadeira para cama (equivalentes são combinações com mais que 1 SF 4+, ou piramidal grau 5 isoladamente)	
7,5	Consegue apenas dar poucos passos. Restrito á cadeira de rodas. Necessita ajuda para transferir-se (equivalentes são combinações com mais que 1 SF grau 4+)	

Escore	Características	Escore Total
8,0	Restrito ao leito, mas pode ficar fora da cama. Retém funções de autocuidado; bom uso dos braços (equivalentes são combinações de vários SF grau 4+)	
8,5	Restrito ao leito constantemente. Retém algumas funções de autocuidade e dos braços (equivalentes são combinações de vários SF grau 4+)	
9	Paciente incapacitado no leito. Pode comunicar, não come, não deglute (equivalentes é a maioria de SF grau 4+)	
9,5	Paciente totalmente incapacitado no leito. Não comunica, não come, não deglute (equivalentes são quase todos de SF grau 4+)	
10	Morte por esclerose múltipla	
TOTAL		

Anexo 3

Universidade Federal da Bahia
C-HUPES - Serviço de Imunologia
Rua João das Botas, s/n - Canela 40110-160 Salvador - Bahia - Brasil

Tel.: (55 71) 3237-7353/3339-6320 FAX: (55 71) 3245-7110

imuno@ufba.br / edgar@ufba.br

Edgar M. Carvalho

Chefe Serviço de Imunologia

Salvador, June 17th, 2015

Eric Klein, MD

Editor-in-Chief, UROLOGY

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Dear Editor,

Enclosed please find the file of the manuscript **"**Risk factors for atherosclerosis in HTLV-1 infected patients with erectile dysfunction**",** to be submitted for publication in *Urology*. This study is original and has not been and will not be submitted for publication elsewhere while under evaluation by *Urology*. We declare that there is no relationship or support which might be perceived as constituting a conflict of interest. Moreover, we confirm that all authors participated in the study and concur with the submission and agree with subsequent revisions submitted by the corresponding author.

Sincerely yours,

Edgar M. Carvalho Rosana C. P. de Andrade José A. Neto

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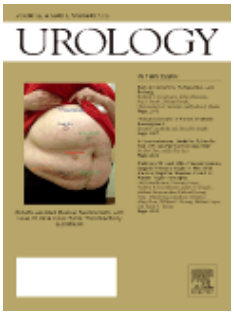

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