The Significance of the Nucleic Acid Test (NAT) to Prevent Viral Contamination in Musculoskeletal Tissue Transplantation

A importância da realização do teste de ácidos nucleicos (NAT) para a prevenção de contaminação viral nos transplantes de tecidos musculoesqueléticos

Carlos Alexandre Curylofo Corsi[1] Alan Vinicius Assunção Luiz[2] Álefe Saloum Cintra[2]
Katia Carmen Gabriel Scarpelini[1] Rodolfo Leandro Bento[3] Flávio Luis Garcia[3]
Celso Herminio Ferraz Picado[3] Luís Gustavo Gazoni Martins[3]

[1] Human Tissue Bank, Hospital das Clínicas, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, SP, Brazil
[2] Escola de Enfermagem de Ribeirão Preto, Ribeirão Preto, SP, Brazil
[3] Hospital das Clínicas, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo. Ribeirão Preto, SP, Brazil

Address for correspondence Carlos Alexandre Curylofo Corsi, Rua Bernardino de Campos, 1000, Centro, Ribeirão Preto – SP, Brazil, CEP: 14015-130 (e-mail: carlos_ccorsi@hotmail.com).

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Abstract

Objective The present study aims to highlight the significance of the nucleic acid test (NAT) for musculoskeletal tissue donation and to compare the sensitivity of this test on the different available platforms.

Method The present study is a retrospective survey in a human tissue bank database and an integrative literature review encompassing the last 10 years. The PubMed portal and the SCOPUS, CINAHL, and Web of Science databases were queried for articles.

Results We found no specific studies on the use and sensitivity of NAT in braindead tissue donors. The information presented in the present study consists of specific contents intended for the Brazilian Blood Transfusion Network (Hemorrede Transfusional Nacional, in Portuguese) and internal retrospective data from a tissue bank located at a city in the state of São Paulo, Brazil.

Keywords
- donor selection
- nucleic acid test (NAT)
- tissue donors
- tissue transplantation
- tissue bank

Multicentric study performed by the Human Tissues Bank from Hospital das Clínicas, Faculdade de Medicina de Ribeirão Preto (HCFMRP/USP) and Escola de Enfermagem de Ribeirão Preto (EERP/USP), Ribeirão Preto, SP, Brazil.

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Conclusions The NAT is effective in blood samples from living patients. However, since biochemical reactions in braindead patients can be different, specific research, platforms, or both are crucial to tissue banks.

Resumo

Objetivo Evidenciar a importância da realização do teste de ácido nucleico (NAT, na sigla em inglês) para doação de tecidos musculoesqueléticos, assim como comparar a sensibilidade deste exame nas diferentes plataformas existentes no mercado.

Método Trata-se de um levantamento retrospectivo no banco de dados de um determinado Banco de Tecidos Humanos e de uma revisão integrativa da literatura, operacionalizada nos últimos 10 anos. As buscas de artigos ocorreram no portal PubMed e nas bases de dados SCOPUS, CINAHL e Web of Science.

Resultados Não foram encontrados estudos específicos sobre a utilização e a sensibilidade do exame NAT em pacientes doadores de tecidos com morte encefálica (ME), sendo as informações apresentadas no presente estudo conteúdos específicos destinados à Hemorrede Transfusional Nacional e aos dados retrospectivos internos de um Banco de Tecidos do interior do estado de São Paulo, Brasil.

Conclusões O exame NAT se apresenta efetivo em amostras de sangue de pacientes vivos. Porém, reações bioquímicas em pacientes com condições de ME podem se apresentar de formas diferenciadas, tornando-se indispensáveis a realização de pesquisas específicas e/ou a indicação de plataformas aos Bancos de Tecidos.

Palavras-chave
- seleção de doadores
- teste de ácido nucleico (NAT)
- doadores de tecidos
- transplante de tecidos
- banco de tecidos

Introduction

Since the approval of the Collegiate Board Resolution (RDC, in the Portuguese acronym) number 55, of December 11, 2015, providing for good practices in human tissue banks for therapeutic use, ratified by the Technical Note of the Brazilian National Health Surveillance Agency (ANVISA, in the Portuguese acronym) number 007/2017 on guidelines for laboratory screening of deceased human tissue donors for therapeutic use, the nucleic acid test (NAT) for viral molecular markers detection became mandatory in all musculoskeletal tissue donors.[1,2]

These guideline changes affect human tissue banks all over Brazil, validating their attributions and operational procedures. In addition, they establish the specific competencies and functions for each bank profile. Eligible donor selection requires strict quality control, and these guidelines refine the inclusion and exclusion criteria of deceased donors regarding clinical, social, and serological screening.[3]

Clinical screening for tissue and solid organ donation occurs after identifying the potential donor and analyzing their medical record for underlying diseases precluding the procedure by the intrahospital transplant team (CITH, in the Portuguese acronym) and the Organ Procurement Organization (OPO, in the Portuguese acronym). Then, clinical tests must attest brain death (BD). These specific tests aim to diagnose the total absence of encephalic blood perfusion or metabolic or electrical brain activity or both.[2,3]

Complying with other clinical exclusions provided for by law, braindead subjects become potential donors for organs such as the heart, lungs, liver, kidneys, pancreas, and intestine, in addition to tissues including corneas, musculoskeletal tissues (bones, tendons, and cartilage), skin, heart valves, and vessels. Patients with circulatory death (cardiorespiratory arrest) are potential tissue donors alone. The current legislation supports these criteria, which depend on the time of physiological ischemia for collecting each organ, tissue, or both.[1,3]

After completing the initial clinical screening, the team contacts the family for social screening and obtains a favorable (or not) consent to the donation, followed by the signature of the donation term. Then, the identified subject becomes a potential organ and tissue donor. The OPO reports all assessments to the Transplant Center, highlighting the eligibility of the donor and indicating elements that may represent a total lack of risks for recipients. Next, the facility recruits an organ recovery team.[1,2]

However, regarding the serological screening to identify potential viral agents in human organ and tissue donors, NAT has a different specificity in each donated tissue (except for corneas), and its performance is mandatory.[1–3] Ocular tissue banks can request a NAT for human immunodeficiency virus (HIV) and hepatitis C virus (HCV) detection in corneal donors instead of a conventional serological test.[2]

HIV, hepatitis B virus (HBC), and HCV antigens detection uses a real-time quantitative/qualitative polymerase chain reaction (RTq-PCR) in a pool of six blood samples from the donor. This procedure reduces the time of the immunological window for contamination when compared with other tests such as the enzyme immunosorbent assay (ELISA).[2,3]

The RTq-PCR technique repeatedly duplicates polymerase chains from DNA, RNA, or both in vitro to generate sufficient quantities for several analyses. Therefore, it is fast and specific, and results are available in a few hours.[4,5]

Today, the Brazilian Unified Health System (SUS, in the Portuguese acronym) performs NAT in all blood samples donated to centers across the country. Donor screening in the blood banks of the Brazilian Blood Transfusion Network legally requires NAT performance to assure the harmlessness of the blood donation process.[6,7]

Human tissue donation constitutes one of the best therapeutic options today. The social and clinical selection of organ donors must be rigorous to favor the quality of life and safety of recipients. In addition, serological screenings must be more sensitive and effective to ensure the safety of recipients and transplant teams.[8]

Since it is crucial to highlight the use and effectiveness of NAT, the present study reports its findings in musculoskeletal tissue donors with brain death by an integrative review of the literature and a survey of serological data from a human tissue bank.

Method

The present study is an integrative literature review (ILR) permeating the central theme and a retrospective survey of data from all NAT performed on donors from a human tissue bank in a city in the state of São Paulo, Brazil.

Queries used descriptors and keywords, both controlled and not controlled, permeating the theme to retrieve original articles published within the last 10 years in English, Portuguese, or Spanish.[9,10]

We selected the controlled descriptors (DeCS) and MeSH from Biblioteca Virtual em Saúde (BVS, in the Portuguese acronym) and the National Center for Biotechnology Information (NCBI). Next, we inserted not controlled descriptors, keywords, or both not found within the DeCS or MeSH terms. These inclusions allowed the authors to do queries in each respective database, increasing the field of investigation.[11] ►**Table 1** shows these descriptors.

Article queries were conducted at the PubMed portal and at the SCOPUS, CINAHL, and Web of Science databases. We identified the best query strategy and amount of search for each database considering the specificity of their interfaces and using both controlled and not controlled descriptors.

Due to the emerging discussion on the subject, we chose a sample cut from the last 10 years (2011 to 2021) due to the extreme relevance of the theme. In addition to original articles, dissertations, and theses published within this period, we included quantitative and qualitative studies and experience reports. We excluded protocols, operational procedures, editorial letters, review articles, and papers about NAT in blood donors, organ donors, or donors of other nonmusculoskeletal tissues.

Within the scope of methodological, scientific rigor, and research replicability, we adopted a previous organization protocol for the present ILR.[8] This protocol follows the six steps for evidence-based practice (EBP): 1. Formulation of the guiding question; 2. Sampling or literature query; 3. Data extraction; 4. Critical analysis; 5. Analysis and synthesis of the review data; 6. ILR presentation. Eventually, we prepared a descriptive report of our findings.[9,12,13]

We determined the guiding question using the PICO strategy, in which P = Participants (musculoskeletal tissue donors), I = Intervention (NAT), and CO = Outcome (effectiveness and significance).[14] Thus, the guiding question was: "What is the significance of NAT in musculoskeletal tissue donors?".

Thus, using different combinations of descriptors, keywords, and Boolean terms, we defined the query strategies in the most appropriate databases according to the guiding question to obtain studies for the present research.

We chose specific query strategies for each database. We conducted the entire methodological sequence, query presentation and rigor, and findings description following a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart adapted by us.[13]

Two reviewers performed the queries independently and asynchronously using all the methodological steps recommended by PRISMA. Then, they obtained potentially eligible studies for the ILR and sent them consecutively to a third reviewer. This third reviewer, an expert on the subject, decided on any selection divergence between the first two reviewers and defined which articles were relevant for this ILR.

Table 1 Catalog of controlled (DeCS and MeSH) and not controlled descriptors used in the operationalization of database queries

Acronym	Controlled descriptors	Not controlled descriptors
P	Donor selection Tissue donors	Human tissue donation Musculoskeletal tissues Bone transplant Bone donation Serological screening
I	Polymerase chain reaction Real-time polymerase chain reaction HIV Hepatitis C Hepatitis B	NAT Nucleic acid test
Co	Tissue transplantation Tissue banks	

Abbreviation: NAT, nucleic acid test.

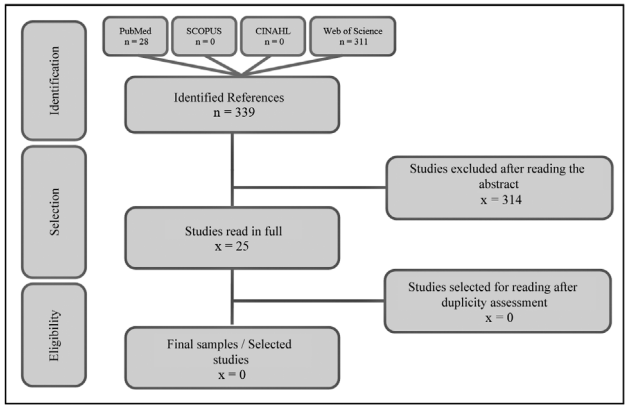

Fig. 1 Sample of database queries based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Source: Authors, adapted.[12], Figura 1–Operacionalização e seleção dos artigos nas bases de dados, com base no PRISMA = ►**Fig. 1**–Operationalization and selection of articles in the databases based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), Identificação = Identification, Seleção = Selection, Elegibilidade = Eligibility, Referências Identificadas = Identified References, Estudos lidos na íntegra = Studies read in full, Amostras finais / Estudos selecionados = Final samples / Selected studies, Excluídos após leitura do resumo = Studies excluded after reading the abstract, Selecionados para leitura após avaliação de duplicidade = Studies selected for reading after duplicity assessment, Fonte: Autores, adaptado.[12] = Source: Authors, adapted.[12]

The queries used links available on the portal of an integrated electronic system connected to the Virtual Private Network (VPN) application from a university in the state of São Paulo. The process of article selection used the Rayyan website (https://www.rayyan.ai/) to help blind systematic and integrative reviews and meta-analyses. Queries were conceived and organized in advance and conducted on a single day in November 2021.

In addition, we performed a retrospective documentary study of serological tests from musculoskeletal tissue donors. This information was on the internal database of a human tissue bank and referred to the period from February 13, 2016, to November 30, 2021.

GraphPad Prism software version 8.0 (Graphpad Software Inc., San Diego, CA, USA) performed the statistical analysis. The collection of NAT findings allowed an analysis of the frequency of these data in our population. Results were expressed as total number and percentage. The technical board from the human tissue bank authorized and approved the present analysis.

Results

Integrative Literature Review (IRL)

The query on the 4 databases within the established timeframes identified and selected 339 articles for reading. During this selection stage, we read the abstracts, resulting in the exclusion of 314 papers and leaving 25 studies for full reading. At the eligibility stage, we read the selected studies in full and excluded 15 papers, which left 10 studies for the last stage of inclusion. However, after applying the inclusion and exclusion criteria, no study was eligible for our ILR. A PRISMA flowchart describes the identification, selection, eligibility, and inclusion processes (►**Fig. 1**).[15]

This means we did not find any specific study regarding the significance and sensitivity of NAT in braindead musculoskeletal tissue donors. The current literature refers to NAT performed in bone marrow, corneas, and solid organ donors.

Documentary analysis (retrospective study)

In total, there were 96 effective donors and musculoskeletal tissue recovery procedures between 2013 (the beginning of the tissue bank activities) and 2021 (the current period). Eighteen of these subjects underwent NAT. ►**Table 2** shows yearly NAT data.

Our human tissue bank works with two types of musculoskeletal tissues: femoral head donation after total hip arthroplasty (live donor), and femur, tibia, fibula, tendons, and lower limb cartilages after solid organ donation (BD donors). Complying with the legislation, all donors undergo a mandatory serology, while BD donors undergo NAT in addition to the conventional serological tests.[1,2] Therefore, in this period, the bank recovered 78 tissues from living donors and 18 tissues from BD donors; these last subjects underwent a NAT.

Discussion

Due to the scarcity of articles in the literature, the information discussed below comes from package inserts from NAT kit platforms, contents from the Brazilian Ministry of Health intended for the Brazilian Blood Transfusion Network, and the course "Laboratory screening and quality control in blood, tissues, cells, and organs – Molecular Biology II" from the Brazilian Health Regulatory Agency (ANVISA, in the Portuguese acronym).[16]

The approval of Ordinance n° 112/2004 led to NAT implementation for blood bag screening in Brazilian National Hemotherapy Services. A public amendment between the

Table 2 Total numbers of tissue donors and nucleic acid tests performed per year

	Total	(%)	Male	(%)	Female	(%)
2013–2021						
Total number of donors per year	96	100%	52	54%	44	46%
Total number of NATs performed	18	100%	9	50%	9	50%
Samples positive for HBC, HCV, or HIV	0	-	-	-	-	-

Abbreviations: HBC, Hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NAT, nucleic acid test.

Table 3 Immunological windows for each test.

Infectious agent	Serology (days)	NAT (days)
HIV	28–30	10–12
HCV	70	10–12
HBC	59	10–12

Abbreviations: HBC, Hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NAT, nucleic acid test.
Source: Authors, adapted.[15,16]

SUS and the Instituto de Tecnologia em Imunobiológicos – Bio-Manguinhos/Fiocruz (Rio de Janeiro, RJ, Brazil) created and assured NAT funding. This amendment resulted in the development of a Brazilian RTq-PCR/NAT platform, reducing the cost and facilitating access to the new technology.[6]

The NAT is an amplifier of nucleic acid sequences from the viral genome, allowing the detection of specific features. Its use reduces the days of the immunological window for contamination (►**Table 3**).

This timeframe usually spans from the initial phase of infection (antigens) to the establishment of immune responses (antibodies). During this window, conventional ELISA serological tests do not detect the presence of antibodies. Therefore, NAT minimizes the risk of recipient contamination because it is a faster and more sensitive test.[17]

In addition to the Brazilian test platform (NAT/Bio-Manguinhos), there are two other imported tests on the market with the same purpose (manufactured by Roche and by Abbott) but with different detection sensitivities (►**Table 4**).

Other than sensitivity, the main difference between these tests refers to cost-benefit;[16] because the Brazilian test is registered within the Ministry of Health/ANVISA, it is more accessible in the public healthcare network through SUS, and its distribution is free of charge.[18]

However, it is worth mentioning that all NAT platforms, according to their package inserts, are validated and intended specifically for (live) blood donors.[4,18,19]

An exception and significant particularity between these platforms refer to the Cobas test platform (Cobas TaqScreen MPX Test, version 2.0; Roche Holding AG, Basel, Switzerland). This test has a validation protocol for blood samples from cadaveric donors (in cardiac/cardiorespiratory arrest). However, the manufacturer states that test of cadaveric samples requires an adjacent kit, the Cobas TaqScreen Cadaveric Specimen Diluent Kit.[15,19]

Table 4 Nucleic acid test sensitivity in three different platforms

NAT kit	HIV (IU/mL)	HCV (IU/mL)	HBC (IU/mL)
Bio-Manguinhos® (FIOCRUZ)	300	300	50
Cobas® (Roche)	50	11	4
Abbott®	40	12	10

Abbreviations: HBC, Hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IU, international units; mL, milliliters; NAT, nucleic acid test.
Source: Authors, adapted.[15–17]

In September 2021, the ANVISA issued a new Resolution, RDC 564/2021.[20] The new document amends RDC No. 55, from December 11, 2015, providing for good practices in human tissues for therapeutic use and introducing some changes. Among these changes, Article 114 highlights that the diagnostic tests used must be registered within ANVISA. In addition, the use of in vitro diagnostic products applies to living and braindead tissue donors. Their methodologies must be indicated for screening either these donors or blood donors.

Deceased donors in cardiorespiratory arrest require specific in vitro diagnostic products whose instructions for use indicate their suitability in samples from these subjects. If a product with this specification is unavailable in the Brazilian market, the use of a kit for live or braindead donors is acceptable but must be duly registered and justified.[20]

As the final responsible for the safety and quality of services, tissue banks must guarantee the feasibility of the test and especially the safety of products provided for therapeutic use.[21,22] Thus, it is critical to know the methodology of each kit, its respective sensitivity and immunological window, and the findings for donor traceability and recipient safety.

The limitation of the present study is the lack of relevant specific articles on the theme proposed for the ILR even after querying the most relevant databases. Despite these limitations, the convergence of the thematic scope when discussing other selected studies stands out, as well as the diversity/sensitivity of the methods of each test. The novelty in correlating the two fields of study in the practical application and decision-making process of tissue banks is also noteworthy since these fields remain little explored.

Conclusion

The NAT is effective in detecting viral loads in blood samples from live donors on all available platforms (both national and international).

With this in mind, we require further specific research on NAT in human tissue donors. Its performance by tissue banks is mandatory according to RDC 55/2015, ANVISA Technical Note n° 007/2017, and RDC 564/2021, or as regulatory agencies indicate specific platforms.

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Conflict of Interests
The authors have no conflict of interests to declare.

Contributions of the Authors
Each author contributed individually and significantly to the development of the present article. Corsi C. A. C.

conceived and planned all the activities resulting in the study and participated in the review process, data collection, discussion, and analysis. AVAS wrote the manuscript, revised its successive versions, and participated in the database query. Cintra A. S. wrote the manuscript, revised its successive versions, and participated in the database query. Scarpelini K. C. G. wrote the manuscript, revised its successive versions, and participated in the data collection and analysis of the retrospective study. Bento R. L. wrote the manuscript, revised its successive versions, and participated in the data collection and analysis of the retrospective study. Alves C. C. S. wrote the manuscript, revised its successive versions, and participated in the data collection and in the analysis of the retrospective study. Garcia F. L. corrected and approved the final version. Picado C. H. F. corrected and approved the final version. Martins L. G. G. participated in the elaboration of the study, in addition to correcting and approving the final version.

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