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ORIGINAL ARTICLE

Association between Insulin use and Infective Endocarditis: An Observational Study

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Abstract

Background: The association between Diabetes Mellitus (DM) and Infective Endocarditis (IE) is controversial in the literature, since many controversial results have been published. However, when evaluating specifically the evidence on IE and individuals with DM using insulin, we found only two observational studies that considered this variable, with discordant results regarding the prognosis and prevalence of *Staphylococcus sp* in insulin users compared to non-users. Despite the lack of evidence, in clinical practice the insulin use could be interpreted as minor criteria "injection drug use", using the modified Duke criteria for IE diagnosis.

Objectives: To compare the microbiological and valvar profile, as well as the outcome of non-diabetic and diabetic patients with IE who were insulin users or not.

Methods: This was an observational, analytical and retrospective study of patients diagnosed with IE between 2003 and 2015 in three tertiary care centers. A total of 211 patients were included, of which 17 were diabetics and 9 were insulin users. Patients were compared using the Shapiro-Wilk normality test and Fisher's exact test, with a significance level of 5%.

Results: The mortality from IE in diabetic individuals was higher than that of non-diabetic patients, but with no statistical significance (35.29% vs. 21.1%; p = 0.221), even when the groups were divided into insulin-user diabetic, non-insulin user diabetic and non-diabetic patients (33.3% vs. 37.5% vs. 21.1%, p = 0.229). There was a difference regarding the prevalence of IE caused by *S. aureus* (57.1% vs. 14.3% vs. 17.4%, p = 0.029) and the involvement of the tricuspid valve (33.3% vs. 0.00% vs. 10.0%, p = 0.034) among insulin users.

Conclusion: In our sample, insulin use or the presence of DM did not mean higher in-hospital mortality from IE. It is not possible to generalize the microbiological and valvar findings due to the lack of studies evaluating insulin users in IE; however, particularities have been previously reported and may indicate a different behavior of IE in these patients. New studies considering the insulin use variable are required to elucidate the association between DM and IE. (Int J Cardiovasc Sci. 2019; [online].ahead print, PP.0-0)

Keywords: Diabetes Mellitus; Insulin; Inyeccion; Infections; Heart Valve Diseases; Endocarditis, Bacterial.

Introduction

Infective Endocarditis (IE) is an infectious condition with high mortality that develops when bacteremia and endocardial tissue invasion occurs, usually in previously damaged cardiac valves. Several conditions have been associated with IE, such as congenital and rheumatic heart diseases, presence of prosthetic valves, prior IE and Diabetes Mellitus (DM).[1-4] DM is a high-prevalence disease, with an estimated 11.9 million affected individuals in Brazil and 387 million in the worldwide population.[5] It is a condition that leads to immunosuppression and, therefore, predisposes to several infectious complications.[6]

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The association between DM and IE is still controversial in the literature. DM has been indicated as an independent predictor of in-hospital mortality in the studies by Chu et al.[3] and Chrillo et al.,[7] and according to Movahed et al.,[8] IE was more prevalent in patients with Type II DM, when compared to non-diabetic patients. On the other hand, although Moreno et al.[9] and Wallace et al.[10] found higher mortality values in diabetic patients with IE in relation to non-diabetic ones, there was no statistical significance to corroborate this association. Other authors have shown that DM was associated with a higher risk of septic shock in IE, but an association with higher mortality was not observed.[11]

However, regarding the use of insulin by diabetic patients and a possible association with IE, there was little evidence in the literature that considered this variable; only two observational studies did it, one carried out by Duval et al.[12] and another by Olmos et al.[11] The first one showed that insulin users showed significant differences regarding in-hospital mortality and the proportion of IE by *Staphylococcus sp* when compared to DM patients receiving an exclusive oral hypoglycemic drug and non-diabetic patients. The results of the second study were discordant, since there were no differences in prognosis and microbiology. It should be noted that the study by Olmos et al.[11] included only cases of IE in the left heart chamber.

For the diagnosis of IE, the Duke Criteria were proposed by Durack et al.[13] in 1994, which represented an advance in the understanding of IE and which included "intravenous drug use" as a minor criterion. However, Li et al.,[14] in 2000, proposed changes that gave rise to the modified Duke Criteria, with the minor criterion "intravenous drug use" being replaced by "injectable drug use".

Therefore, by definition,[15] any subcutaneous, intramuscular or intravenous injectable substance would also be considered a minor and predisposing criterion for IE, such as insulin. We emphasize that the reason for the change was not addressed by Li et al.[14]

Moreover, considering the pathophysiological aspects of IE, in which bacteremia has an essential role, it is possible that the use of subcutaneous insulin has characteristics that are close to those of the group of patients who use intravenous drugs. The correlation between intravenous drug use and IE is explained by the introduction of microorganisms and particles into the circulation during the injection, which damage and colonize the heart valves.[16]

In the case of insulin use, despite the subcutaneous route of administration, it would be plausible the hypothesis of bacteremia occurring in certain situations, such as hematoma at the injection site, a frequently described complication[17-19] with the use of inadequate techniques and one that represents vascular damage associated with a solution of continuity with the skin microbiota. In fact, Tuazon et al.[20] have shown that insulin use increases the risk of mucocutaneous colonization by *S. aureus*.

Skin infections such as abscesses have also been described in injection sites in insulin users, and according to Binswanger et al.,[21] the subcutaneous space can be colonized by multiple microorganisms that are introduced by non-sterile drug injections. The study by Lipsky et al.[22] demonstrated bacteremia in 15 to 19% of patients with this type of infection and the most often involved microorganism was *S. aureus*.

Patients who are insulin-users also have the concomitant need for frequent self-monitoring of blood glucose levels through finger blood collection, which could facilitate bacteremia, as the capillary bed is exposed to the external environment. Cases of sepsis and osteoarthritis due to abscess focus in the fingers of patients who were inadequately self-monitoring blood glucose have already been reported.[23,24,25]

Thus, the aim of the study is to evaluate and compare the microbiological, valvular and outcome aspects of IE in diabetic patients who are insulin users or non-insulin users or are not diabetic, in addition to comparing the results with the current literature.

Method

Study population

The population consisted of 211 patients with probable or definitive IE admitted at in three tertiary care centers in the municipalities of Belo Horizonte and Ipatinga, state of Minas Gerais, Brazil, between 2003 and 2015.

The inclusion criteria were: patients admitted between 2003 and 2015 in three hospitals, who were diagnosed with definitive or probable IE, according to the modified Duke criteria.[13] Patients who met the criteria for Definitive or Probable IE were included in the database. The exclusion criteria were: patients who were transferred to another tertiary care center or who were still hospitalized during the data collection period. Medical records with insufficient data were also excluded.

The Free and Informed Consent was waived, considering the retrospective design of the study, which was approved by the Research Ethics Committee of *Faculdade Ciências Médicas de Minas Gerais*, under number CAEE 1.856.064.

Study design

This is an observational, retrospective and cross-sectional study. It has an analytical aspect,[26] as it compares and applies statistical tests to diabetic patients who are insulin users, non-insulin users and non-diabetic patients. A microbiological profile was collected according to the blood culture or valvular culture results that were described in the medical records. The site of EI involvement was collected according to transthoracic, transesophageal echocardiography or perioperative findings.

Patients who used insulin only during hospital stay were not included in the insulin-user group. Any type of subcutaneous insulin used by the patients was considered (NPH, Regular, Glargine, Ultra-fast, Lispro, Aspart, etc.). The medical records that showed any doubts, of any nature, were evaluated again by the author. All data collected were entered into an Excel worksheet.

Sample size

The sample was calculated to test the proportion of diabetics among patients with infective endocarditis. Considering a significance level of 5% and a minimum power of 80%, using the result of a reference study,[7] to detect a minimum difference of 6.6% in the proportion of diabetics, at least 210 patients with IE would be required.[27]

Data analysis

The categorical variables were shown as numbers and percentages, and the numerical variables as mean ± standard deviation (SD). The numerical variables were submitted to the Shapiro-Wilk normality test. The association between the analysis groups and the variables of interest was performed using a multinomial logistic model. The comparison of means was performed through one-way analysis of variance. The association between the type of diabetes and the presence of comorbidities was assessed using Fisher's exact test. The analyses were carried out using the free program R, version 3.3.2, with a significance level of 5%.

Results

Epidemiological and prognostic aspects are shown in Table 01. A total of 211 patients were included in our analysis, 110 from Belo Horizonte and 101 from Ipatinga. The mean age of the patients was 46.6 ± 18.8 years and 70.6% of the them were males. Regarding the outcome, the number of deaths was 47, representing a mortality rate of 22.3%. When analyzing the patients from Belo Horizonte and Ipatinga separately, it can be observed that the mortality rate was 20% and 20.7%, respectively.

Table 2 shows the results regarding the microbiological profile of our sample. Considering the positive blood

Table 1 - Epidemiological and prognostic aspects of hospitalized patients with Infective Endocarditis

Characteristic	IUD (n = 9)	NIUD (n = 8)	ND (n = 194)	Total (n = 211)	p-value
Age	56.9 ± 13	56.3 ± 9.7	45.7 ± 19.1	46.6 ± 18.8	0.071*
Male gender	4 (44.4%)	5 (62.5%)	140 (72.2%)	149 (70.6%)	0.066†
Definitive IE	6 (66.6%)	6 (75%)	106 (54.6%)	118 (55.9%)	0.277†
Blood cultures performed	9 (100%)	8 (100%)	160 (82.5%)	177 (83.9%)	-
Positive blood culture	7 (77.8%)	7 (87.5%)	92 (47.4%)	106 (50.2%)	0.057†
Defined location	9 (100%)	6 (75%)	192 (99%)	208 (98.6%)	-
Deaths L	3 (33.3%)	3 (37.5%)	41 (21.1%)	47 (22.3%)	0.229†

*ND: non diabetics; NIUD: non-insulin-user diabetics; IUD: insulin-user diabetics. The superscripts indicate the method used for the association analysis: * One-way analysis of variance; † multinomial logistic model. [L]Comparing the mortality of diabetics and non-diabetics, there was no statistical significance according to Fisher's exact test (p = 0.221).*

cultures, our results showed a higher prevalence of the *Staphylococcaceae genus* (37.7%), almost equally distributed as 19.8% *S. aureus* and 17.9% of coagulase-negative *Staphylococcus*.

We emphasize that the prevalence of *S. aureus* was similar when we evaluated the two cities separately, with 18.6% in Ipatinga and 20.6% in Belo Horizonte. *Streptococcus spp* represented the second most prevalent genus, estimated at 29.2%, followed by *Enterococcus spp* with 13.2% and other microorganisms in 9.4% of the time. The blood culture was shown to be positive in the medical records, but without specifying the microorganism in 13.2% of the patients.

The location of the IE is shown in Table 3. The native valves were the most affected site in the general sample, representing 149 (70.6%) patients, most of them in the mitral valve (41.7%), followed by the aortic valve (26.5%), tricuspid (10%) and pulmonary (1.4%) valve. The valvular prostheses were infected in 51 (24.2%) patients, pacemaker cable in 9 (4.3%) and 6 (2.8%) were infected in other places such as the right atrium, pulmonary arteries, superior vena cava ostium or interventricular septal defect.

There were 194 non-diabetic and 17 diabetic patients, of which 9 (52.9%) were insulin users and 8 (47.1%) used only oral hypoglycemic drugs. The data showed 35.29% of mortality in diabetics and 21.1% in non-diabetic patients, with no statistical difference (p = 0.221). When considering diabetics who used or did not use insulin, the observed mortality was 33.3% and 37.5%, respectively, and the statistical tests did not show a significant difference in relation to this variable (p = 0.229).

The microbiological comparison between the subgroups showed a higher proportion of *S. aureus* in insulin users than in the non-diabetic group, with a statistical significance (p = 0.029), whereas *Streptococcus spp* was the most common microorganism in the diabetic patients receiving oral medication and in non-diabetic patients.

The native mitral valve was the most often affected in patients who did not use insulin, non-diabetic or diabetic patients, with 42.8% and 25%, respectively. In the diabetic patients who used insulin, we observed that the mitral valve showed the same prevalence as the tricuspid valve, calculated as 33.3%. We emphasize there was a statistical significance between tricuspid valve involvement (p = 0.034). The aortic valve was the second most affected in the total sample, in 26.5% of the patients, which was also observed in non-diabetic patients, with 27.8%.

There was a higher prevalence of individuals with unidentified sites among diabetics who were non-insulin-users and non-diabetic patients (p = 0.031).

Table 04 shows several characteristics of the diabetic patients in our sample that could influence prognostic, microbiological and valvular aspects in the groups of insulin users or non-users. The statistical analysis showed homogeneity between the two groups, which improves the internal validity of the comparison. However, it

Table 2 - Microbiological profile of 106 patients with a positive blood culture diagnosed with Infective Endocarditis

Microorganism	IUD (n = 7)	NIUD (n = 7)*	ND (n = 92)*	Total (n = 106)*	p-value
Staphylococcus spp	5 (71.4%)	2 (28.6%)	33 (35.9%)	40 (37.7%)	0.133†
S. aureus	4 (57.1%)‡	1 (14.3%)	16 (17.4%)‡	21 (19.8%)	0.029†
Coagulase negative S§	1 (14.3%)	1 (14.3%)	17 (18.5%)	19 (17.9%)	0.723†
Streptococcus spp//	-	3 (42.9%)	28 (30.4%)	31 (29.2%)	0.217†
Enterococcus	-	-	14 (15.2%)	14 (13.2%)	-
Others¶	1 (14.3%)	1 (14.3%)	8 (8.7%)	10 (9.4%)	0.535†
Not specified#	1 (14.3%)	2 (28.6%)	11 (12%)	14 (13.2%)	0.519†

*ND: non diabetics; NIUD: non-insulin-user diabetics; IUD: insulin-user diabetics. * Some patients had more than one microorganism growing in the blood culture; † Association evaluated via multinomial logistic model; ‡ Indicates pairs with significant difference (p < 0.05); §S. epidermidis, S. warneri, S. haemoliticus, S. lugdunensis, S. capitis; //S. pneumoniae, S. pyogenes, S. sanguinis, S. mitis; ¶ Haemophillus spp, Candida spp, Proteus mirabilis, Proteus penneri, E. coli, Enterobacter sp, Klebsiella sp,, Achromobacter xylosoxidans, Morganella morganii, Stenotrophomonas maltophilia, Facklamia hominis; # Blood culture was positive, but the microorganism was not specified.*

Table 3 - Cardiac structures affected in 211 patients with Infective Endocarditis

Location	IUD (n = 9)	NIUD (n = 8)	ND (n = 194)*	Total (n = 211)*	p-value
Native valves	7 (77.8%)	3 (37.5%)	139 (71.6%)	149 (70.6%)	0.642†
Mitral	3 (33.3%)	2 (25%)	83 (42.8%)	88 (41.7%)	0.369†
Aortic	1 (11.1%)	1 (12.5%)	54 (27.8%)	56 (26.5%)	0.168†
Tricuspid	3 (33.3%)‡	-	18 (9.3%)‡	21 (10%)	0.034†
Pulmonary	-	-	3 (1.5%)	3 (1.4%)	-
Prosthetic valves	1 (11.1%)	3 (37.5%)	47 (24.2%)	51 (24.2%)	0.640†
Pacemaker cable	-	-	9 (4.6%)	9 (4.3%)	-
Others §	1 (11.1%)	-	5 (2.6%)	6 (2.8%)	0.237†
Unidentified location	-	2 (25%)‡	1 (0.5%)‡	3 (0.1%)	0.031†

*IUD: insulin-user diabetics; NIUD: non-insulin-user diabetics; ND: non diabetics; *Some patients showed lesions in more than one place; †Association evaluated via multinomial logistic model; †Indicates pairs with significant difference ($p < 0.05$); § Right Atrium, Pulmonary Arteries, Ostium of the interventricular defect, Ostium of Superior Vena Cava.*

Table 4 - Characteristics of diabetic individuals with Infective Endocarditis according to insulin use

Location	IUD (n = 9)	NIUD (n = 8)	p-value
Health care related IE†	2 (22.2%)	3 (37.5%)	0.620
Systemic arterial hypertension	9 (100%)	7 (87.5%)	0.471
Dyslipidemia	5 (55.5%)	4 (50%)	1.000
CHF NYHA III*	3 (33.3%)	2 (25%)	1.000
Valvulopathy	2 (22.2%)	3 (37.5%)	0.620
Coronary artery disease	2 (22.2%)	3 (37.5%)	0.620
Dialytic chronic kidney disease	2 (22.2%)	2 (25%)	1.000
Non-dialytic chronic kidney disease	1 (11.1%)	1 (12.5%)	1.000
Smoking	3 (33.3%)	4 (50%)	0.637
Alcohol consumption	3 (33.3%)	2 (25%)	1.000

*† According to the definition used by Yang et al.28. We included in this group 4 patients undergoing kidney dialysis and 1 patient in long-term care. It was not possible to evaluate hospitalizations up to 90 days prior to IE manifestations, so this criterion was not used. NIUD: non-insulin-user diabetics; IUD: insulin-user diabetics. The p-values refer to Fisher's exact test. * NYHA Class III Congestive Heart Failure.*

was not possible to reliably collect these same variables for non-diabetic patients in our sample, which could represent a limitation in the comparison with this group.

Discussion

When considering the general data of all 211 patients with IE in our population, regardless of whether or not they were diabetics, findings consistent with large observational studies in the literature can be observed. The multicenter study by Murdoch et al.,[1] with 2781 patients with IE, showed a mortality rate of 18.0%, comparable to the 22.3% in our results. Moreover, the proportion of diabetic patients with IE was 8.0% (n = 17), similar to the 10.0% found by the same study by Murdoch et al.,[1] when only South America was considered.

The microbiological profile evaluated in the literature shows differences according to the affected site. The findings were proportional to those in the study by Murdoch et al.,[1] when considering only South America (n = 254), which showed a predominance of *Streptococcus sp.* in 26.0%, followed by *S. aureus* in 17%, whereas ours results showed 25.0% and 18.0%, respectively. In contrast, Nunes et al.[29] (n = 62) and Ruiz et al.[30] (n = 159), in Belo Horizonte, state of Minas Gerais and Ribeirão Preto, state of São Paulo, respectively, found a higher prevalence of *S. aureus* (32.0% and 27.0%).

In our sample, mortality was higher in diabetic patients, when compared to non-diabetic ones, 33% and 19.5% respectively, but there was no statistical significance (p = 0.221), as reported by Wallace et al.[10] with 36% and 16% and Moreno et al.[9] with 31% and 15%. That is in disagreement with the results of Chrillo et al.[7] and Movahed et al.,[8] who indicated an association between DM and the outcome of IE.

When we attempted to separate the diabetic patients between those who used or did not use insulin, mortality persisted without a statistically significant difference between the two groups, as demonstrated by Olmos et al.[11] On the other hand, Duval et al.[12] obtained a different result, showing that insulin use was a strong and independent predictor of mortality in IE.

According to Wang,[31] the higher mortality rate observed in insulin users reported by Duval et al.[12] occurred because generally there is a higher prevalence of complications in patients with DM, such as coronary artery disease, renal failure, among others. In our sample, the groups of diabetic patients who were insulin users and non-insulin users were similar regarding these characteristics and there was no difference in the outcome, which may corroborate the hypothesis by Wang,[31] i.e., that the clinical evolution is more related to the state of vulnerability associated with DM complications. It is also possible that the type of treatment implemented is a determinant for prognosis, but this variable was not collected in our study and it was not possible to evaluate whether there was any difference between the groups.

We observed specific and relevant characteristics of the IE in insulin users in comparison to the other patients, related to the high prevalence of IE by *S. aureus* and the involvement of the tricuspid valve. In the study by Duval et al.,[12] *S. aureus* also represented the majority of insulin users, but the statistical significance was only observed when the entire *Staphylococcus spp* genus was considered. As for the results of Olmos et al,[11] which studied only cases of left-chamber IE, *S. aureus* was also more prevalent, with 27.6% of cases, but there was no statistical significance.

From the point of view of valvular involvement, the higher prevalence of IE in the tricuspid valve was not consistent with the findings of Duval et al.,[12] since there was no statistical significance in relation to this variable. It should be noted that in the study by Olmos et al.,[11] patients with right-chamber IE were excluded from the sample, which makes this comparison impossible and also raises the question whether this fact could have underestimated the proportion of IE caused by *S. aureus* among insulin users in their study.

It can be observed that the higher prevalence of IE by *S. aureus* and the significant tricuspid involvement among insulin users are similar characteristics to what is described in IE observed in intravenous drug users, a known and well established risk factor for IE. Our results showed 57.1% of IE by *S. aureus* in insulin users, whereas this rate has already been described in the literature as ranging from 64.2% to 82% among intravenous drug users.[1,30,32,33]

Regarding the tricuspid valve involvement,[32,34] rates have been reported as raging from 44% to 46% among intravenous drug users, and a rate of 33.3% was observed in the present study, which is in contrast with that observed in the general population, with 10% in our sample and 7% in South America, according to Murdoch et al.[1]

Study limitations

The present study has several limitations regarding its retrospective design. First, the difficulty in obtaining some information that would be relevant for sample characterization. It was not possible to obtain information on specific characteristics of non-diabetic patients, such as the proportion of patients with health-care related IE[28], which would attenuate the bias of the comparison of the *S. aureus* proportion in this group of patients. It was possible to collect specific characteristics in diabetic patients, but the criterion of previous hospitalization related to health-care related IE[28] was not used.

It was not possible to control for the quality, interval and location of blood collection for cultures, and sometimes the information on how many samples showed bacterial growth was not reported and, therefore, it is believed that some positive blood cultures, especially those in the ones that showed growth of coagulase-negative *Staphylococcus*, the result may be due to contamination.

Blood culture was not performed in 34 patients, which received empirical treatment or who had already started antibiotic therapy at the health services that referred them. It was not possible to collect data regarding the time of DM, glycemic control and quality of IE treatment received, whether surgical or not, which are information that directly reflect the prognosis of these patients.

Additionally, the sample size may be considered insufficient, since there is a considerable difference between the number of non-diabetic and diabetic patients

in our sample. The initial search for medical records through the International Classification of Diseases codes may have underestimated the total number of IE cases that occurred in these hospitals during the assessed period, considering the records may not have been performed in the presence of other diagnoses.

Conclusion

According to our results, diabetic patients did not show higher mortality rates in comparison to the others, even those who used insulin. In turn, we observed a statistically significant difference regarding the higher prevalence of IE by *S. aureus* and the greater involvement of the tricuspid valve among insulin users. Only two studies separately analyzed diabetics with IE who used or did not use insulin, and some of our results are in agreement and others in disagreement with these studies, which makes it difficult to generalize the results.

Nevertheless, it is reasonable to infer that these microbiological and valvular characteristics found in the insulin users of our sample may signal a particular IE profile in these patients. New observational studies considering the insulin use variable are necessary to understand whether these characteristics are identified in observational studies with significant samples and in different locations. Thus, by establishing and controlling the previous insulin use variable, it may be possible to obtain a better understanding of the factors involved in the association between DM and IE, aiming to clarify the current controversy.

Despite the limitations of observational and retrospective studies to confirm causal inferences, the analogy between the microbiological and valvular profile of the insulin user and the intravenous drug user is notable. The analogy is a piece of evidence of contestable strength; however, when associated with the fact that both are injectable substances and could share the same pathophysiological mechanism, it raises a hypothesis to be confirmed or rejected in future studies.

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Author contributions

Conception and design of the research: Bezerra R. Acquisition of data: Bezerra RL, Carvalho TF, Batista RS, Silva YM, Fiuza-Campos B, Castro JHM, Filho RMB, Monteiro PIP. Analysis and interpretation of the data: Bezerra RL, Carvalho TF, Batista RS, Silva YM, Fiuza-Campos B, Castro JHM, Filho RMB, Monteiro PIP. Statistical analysis: Bezerra RL, Alves MC. Obtaining financing: Bezerra RL, Batista RS, Monteiro PIP, Machado ELG. Writing of the manuscript: Bezerra RL. Critical revision of the manuscript for intellectual content: Bezerra RL, Machado ELG, Batista RS, Silva YM, Carvalho TF, Alves MC, Castro JHM.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the *Pesquisa da Ciências Médicas – MG* (CEPCM-MG) under the protocol number 1.856.064. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

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