Syphilis on the rise: A prolonged syphilis outbreak among HIV-infected patients in Northern Greece

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Abstract

Introduction Sexually transmitted diseases (STDs) are a major public health issue in Europe. Numerous outbreaks of syphilis have been described recently and an increased prevalence of high-risk sexual practices has raised concern about the transmission of HIV and other STDs. Similarly, an increase in sexually transmitted infections has been recorded in Northern Greece.

Methods This report describes a recent outbreak of syphilis in people living with HIV. The demographic, clinical, and serologic data of HIV patients diagnosed with syphilis were recorded and analyzed. Data on syphilis incidence from the general population was also compared to HIV patients' data.

Results Fifty-eight HIV-patients of the Infectious Diseases Unit of a tertiary hospital (5.2%) were diagnosed with syphilis during a three-year period (2008-2010). Highly active antiretroviral therapy (HAART) and coexistence of other STDs were independent predictors of syphilis (OR: 2.4, 95CI%: 1.26, 4.63, $p=0.008$; OR: 9.4, 95%CI: 4.49, 19.64, $p<0.001$, respectively). Origin from a country other than Greece ($p=0.005$), and homosexual contact ($p=0.003$), were separate risk factors for syphilis in the general population in the same area.

Conclusion Diagnosis of a sexually transmitted disease in an HIV patient is a crucial clinical event that should trigger the clinician's suspicion for high-risk sexual behavior. Sexual health assessments should be a routine process for HIV patients.

Keywords Syphilis, outbreak, HIV, sexually transmitted diseases, coinfection.

Introduction

Syphilis is a sexually transmitted infection progressing in several stages. Symptoms in primary syphilis may vary, however this stage is considered highly infectious. Without treatment the infection progresses to the second stage, which often manifests with systemic symptoms. Transmission may also occur at this stage and symptoms usually resolve with or without treatment. If untreated, the patient advances to

latent and late (tertiary) syphilis which can affect the majority of organs.¹

Syphilis may augment the rate of HIV acquisition between two- and four-fold and the risk for HIV transmission between two- to nine-fold.² A causal relation between the two diseases can be explained by behavioral factors as well as pathogenic mechanisms, such as facilitation of HIV transmission caused by genital ulceration and inflammation.³ HIV and sexually transmitted disease (STD) coinfection has raised concern as a

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public health issue in the last decade. Studies have indicated multiple facets of this synergistic relationship: people infected with STDs are more likely to acquire HIV, and people coinfecting with HIV and STDs are more likely to transmit HIV.^{4,5}

During the 1980s a reduction in the incidence of STDs was seen in many countries likely due to behavioral changes occurring in response to the emergence of HIV/AIDS.^{6,7} The rise in high-risk sexual practices and migration has contributed to the increased incidence of STDs since 2000. Moreover, advances in epidemiologic surveillance and patient detection methods have led to higher numbers of reported cases.⁸ In Western Europe the reappearance of syphilis was mainly attributed to outbreaks among men who have sex with men (MSM) with novel sexual networks and high-risk sexual behaviours.⁹

The overall rate of syphilis cases in the European Union was 8.2 per 100,000 in 2000. In 2009, 18,279 syphilis cases were reported from 28 European Union countries, with an overall rate of 4.5 per 100,000 population. This decline in rates might be attributed to a significant decrease of cases in numerous countries previously reporting extremely high incidence of syphilis, due to prevention measures.^{10,11} Syphilis was reported almost three times more frequently in males than in females.¹¹ In 2012, nearly 48% of the syphilis cases were reported in MSM.^{12,13} More recent trends (2008–2012) show sharp increase of syphilis, particularly in Western Europe. Increases over 50% were observed in Denmark, Greece and Portugal during 2008–2012.¹⁰ The increase is probably due to the introduction of a new surveillance system and the inclusion of more reporting centers.¹⁰ During

2006–2010 Greece has reported rising rates of syphilis (0.6 to 2.3).¹⁰

HIV infection still affects MSM disproportionately in the European Union, and a remarkable increase in the number of new HIV diagnoses in MSM has been recorded since 2000. Meanwhile, STDs have also re-emerged in this population and the occurrence of several outbreaks especially in HIV-infected MSM,⁹ underlines the high rate of HIV and STD coinfection in this group. Undoubtedly, the existence of other STDs increases the possibility of transmitting HIV infection.^{12–13} Since STDs may represent a cofactor for HIV transmission and on the other hand HIV may alter the clinical presentation of syphilis, their coexistence in specific sexual networks may increase the spread of both infections.^{14,15}

Outbreaks of syphilis in high-risk groups, especially among MSM, drug users and sex workers, are frequent in many countries.¹⁶ Episodic STD outbreaks among HIV seropositive people indicate intermittent risky sexual behavior, concerning STD transmission.¹⁶

Data on syphilis epidemics in Greece have been provided until 2010, with only 11 hospitals providing source data on syphilis cases to the two national reference centers for syphilis (Southern and Northern Greece Reference Centers). Evidence also suggests an increase in syphilis cases recorded in the general population from 2008 to 2010 in Northern Greece.¹⁷

Methods

All adult HIV seropositive patients in the Infectious Diseases Division of AHEPA University Hospital in Thessaloniki Greece, which comprises the National HIV/AIDS Reference Centre of Northern Greece, are routinely screened for syphilis once a year. Those diagnosed as having syphilis from 1st of January 2008 through 31st of December 2010 were studied (demographic characteristics, history, physical examination, clinical data, serologic screening, cerebrospinal fluid [CSF] examination) to assess the stage of their infection. Patient demographics, such as age, nationality, possible route of acquisition for sexually transmitted diseases (including HIV and

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syphilis), HAART use, years of HIV seropositivity and laboratory parameters such as CD4 count and HIV RNA viral load were recorded. Existence of other sexually transmitted diseases (genital herpes infection, gonorrhea, *Chlamydia* infection, donovanosis) was also investigated. Due to an increase in syphilis cases in 2008, the following two years (2009-2010), patients were encouraged to be tested twice a year and testing was also provided to their sexual partners. Moreover further prevention actions were taken to control the outbreak. Already diagnosed syphilis positive patients were excluded from the incident cases of next years, if they reappeared to be syphilis positive. By the time syphilis was diagnosed, repeat tests from the same individual were not included in the analysis.

Syphilis screening was performed using two non-treponemal tests, namely the venereal disease laboratory (VDRL) and rapid plasma reagin (RPR) tests. A positive VDRL was confirmed with the fluorescent treponemal antibody-absorption (FTA-ABS) test. Patient assessment included cardiovascular, ophthalmologic and neurologic evaluation, and cerebrospinal fluid examination (cell profile, VDRL, and FTA-ABS). Both VDRL and RPR test were performed for each patient. Disease stage was determined based on history, clinical findings, and laboratory results. All positive patients are encouraged to get a CSF analysis, especially when their CD4 cell count is below 400 cells/cmm. All patients included in the study had signed an informed consent.

Adults over 18 years old can be tested in the Syphilis Reference Centre of General Population of Northern Greece, maintaining their anonymity. Data from the National Syphilis Reference Centre of General Population of Northern Greece were reviewed for the same time period (2008-2010). These data concerned the gender, age, origin, possible way of transmission, existence of symptoms and results of serologic tests. Sex workers (which are tested frequently twice a year) were excluded from the analysis as well as all HIV positive patients that joined the National Syphilis Reference Centre for syphilis testing. The new

surveillance system for STDs, established in 2009, actively collects data on cases of syphilis and congenital syphilis. Data is collected from hospitals, laboratories and clinicians, in the public and private sector. The EU-2008 case definitions are used. The new system is intended to be comprehensive but does not yet provide national coverage. Underreporting may still exist in some Greek regions. So it was decided that the data from the National Syphilis Reference Centre of General Population of Northern Greece would better describe the trend of syphilis in the population of Northern Greece, to juxtapose syphilis incidence in the general population and in HIV-infected individuals throughout the study period.

Statistical analysis

The odds of syphilis were considered as the dependent variable in logistic regression and its association with other variables was examined. First, univariate analyses were conducted and all significant variables with $p < 0.05$ were considered for inclusion in the multivariable model by forced entry. The odds ratios and corresponding 95% confidence intervals (95%CI) are reported. All reported p -values are two-tailed at a 0.05 significance level; analyses were conducted using SPSS, version 18 (SPSS Inc, Chicago, IL, USA).

Results

HIV population

Of the 1119 HIV patients followed up at our hospital during the study period, 58 (5.2%) were positive for syphilis (Table 1). The entire cohort was serologically tested for syphilis. The vast majority of syphilis patients were MSM (55 patients, 94.82%) with a mean age $\pm$ standard deviation (SD) of 35.65 ± 10.94 years. The mean duration of HIV infection was 3.32 ± 4.35 years and the possible route of syphilis transmission was sexual contact. At the time of syphilis seropositivity, mean CD4 cells count was 440.3 ± 238.9 cells/cmm and mean plasma HIV RNA viral load was $201,903 \pm 382,730$ copies/cmm. Of the 58 patients, 45 (77.7%) were receiving HAART at the time of syphilis diagnosis, and the mean time on HAART was 2.68 ± 4.26 years. HIV and syphilis coinfecting patients' demographics per year of the outbreak are illustrated in Table 1.

Table 1. Demographics of HIV population coinfecting with syphilis

Characteristics of HIV population	2008, n/N (%)	2009, n/N (%)	2010, n/N (%)
Syphilis cases	27/800 (3.3%)	15/1403 (1.07%)	16/1518 (1.05%)
Gender			
Males	26 (96.2)	13 (86.6)	16 (100)
Females	1 (3.7)	2 (13.3)	0 (0.0)
Origin			
Greek	25 (92.5)	15 (100)	15 (93.7)
Immigrants	2 (7.4)	0 (00.0)	1 (6.3)
Mode of transmission			
Heterosexual	1 (3.7)	2 (13.3)	0 (00.0)
Homosexual	26 (96.2)	13 (86.6)	16 (100)
Other/unknown	0 (00.0)	0 (00.0)	0 (00.0)
Age, mean $\pm$ standard deviation	41.2 $\pm$ 9.3 4	32.1 $\pm$ 7.1 1	34.7 $\pm$ 8.8 9

Regarding syphilis stage, the distribution in the HIV population was 26% primary syphilis, 33% secondary syphilis, 37% latent syphilis and 4% neurosyphilis. Most HIV patients were diagnosed with latent, secondary or primary infection during the outbreak period. All 58 syphilis positive patients, consented to undergo a CSF analysis. Of them, only 4% suffered from confirmed central nervous system syphilis infection at diagnosis.

A significantly greater proportion of patients with syphilis were on HAART than patients without syphilis (OR 2.41, 95%CI: 1.25-4.63, $p=0.026$). Furthermore, a significantly greater proportion of patients with syphilis had concomitant STDs than patients without syphilis (OR 9.38, 95%CI: 4.48-19.64, $p<0.001$). There was no association between syphilis and CD4 cell count ($p=0.216$), viral load ($p=0.609$), age ($p=0.943$), mode of transmission ($p=0.484$) or duration of HIV infection ($p=0.693$). In the multivariate logistic model, both HAART and existence of STDs were independent predictors of syphilis, showing that the odds of syphilis were 2.4 times higher in patients with HAART than in

Table 2. Multivariate analysis of all variables in the HIV study population of the ID Unit

	Syphilis(+)	Syphilis(-)	p-value	OR, 95%CI
Gender				
Male	55 (94.8%)	960 (90.3%)	0.258	1.21, 0.52-1.69
Female	3 (5.2%)	103 (9.5%)		
Age, mean $\pm$ SD	35.65 $\pm$ 10.94	38.32 $\pm$ 10.8	0.943	1.00, 0.97-1.02
HAART				
Yes	39 (67.2%)	524 (49.3%)	0.026	2.41, 1.25-4.63
No	19 (32.7%)	539 (50.7%)		
Duration of HAART	2.68 $\pm$ 4.26	2.82 $\pm$ 4.97	0.703	N/A
CD4 cell count/mm³ mean $\pm$ SD	440.3 $\pm$ 238.9	493 $\pm$ 305.1	0.216	0.99, 0.99-1.01
HIV RNA viral load copies/mm³, mean $\pm$ SD	201,903 $\pm$ 382,730	123,831 $\pm$ 550,921	0.609	1.05, 0.86-1.27
Mode of transmission				
Homosexual	55 (94.8%)	944 (89%)	0.477	N/A
Heterosexual	3 (0.05%)	76 (7.2%)		
IDU	0 (0.00%)	2 (1.08%)		
Other/unknown		41 (3.8%)		
Duration of HIV infection, mean $\pm$ SD	3.32 $\pm$ 4.35	3.05 $\pm$ 5.32	0.693	1.01, 0.95-1.03
Concomitant STDs	22 (37.9%)	73 (6.9%)	<0.001	9.38, 4.48-19.64
Multiple sex partners	39 (67.2%)	170 (15.8%)	<0.001	8.75, 3.56-17.62
Unprotected sexual practices	58 (100%)	358 (33.4%)	<0.001	9.40, 4.25-16.52

HAART – Highly active antiretroviral therapy; ID – infectious diseases; IDU – injecting drug use; N/A – not applicable; SD – standard deviation; STDs – sexually transmitted diseases.

Data are presented as n (%), unless otherwise specified

patients not receiving HAART (95CI%: 1.26, 4.63, $p=0.008$) and it was 9.4 times higher in patients with STDs than in patients without STDs (95% CI: 4.49, 19.64, $p<0.001$) – Table 2.

High risk sexual behaviors such as unprotected sexual contacts or multiple sex partners, were remarkably prevalent in the HIV syphilis-positive population. All of the syphilis patients mentioned no use of protection (i.e., condom use), which was statistically significant when compared to the respective proportion of the syphilis-negative adults. Furthermore, the vast majority of syphilis positive patients mentioned exchange of multiple sex partners during the last 6 months compared to negative individuals (67.2 % vs. 15.8%) (Table 2). Five out of the 58 (8.6%) syphilis positive patients were re-infected during the follow up study, but these were excluded from the analysis.

All HIV patients who were found positive for syphilis were offered behavioral counseling from a clinical psychologist. Screening for HIV and syphilis was also offered to their sexual partners. Forty two sexual partners were tested for syphilis and 11 were found to be syphilis positive (26.1%). Twelve of the sexual partners were not HIV positive (28.5%). Subsequently, serosorting between those couples reaches approximately a quarter. Individuals exposed to syphilis within 90 days preceding the diagnosis of primary, secondary, or early latent syphilis in their sex partners were treated. A letter informing that there is an outbreak of syphilis among patients of our HIV unit, providing information about safe sexual practices was administered to all patients during their follow-up visits. Starting with 2009, syphilis testing was offered twice a year.

General population

During the study period, there was also an increased prevalence of syphilis in the general population. An average 15% of the 1273 adults tested were found to be syphilis positive during the same three years of observation. Sex workers and HIV positive adults were not included in the analysis. The characteristics of this population differed from the HIV population in terms of sex, country of origin, age and mode of transmission. More than half of the syphilis positive adults of

the general population tested were diagnosed with concomitant STDs (genital herpes infection, gonorrhea, *Chlamydia* infection, donovanosis) throughout the study period (Table 3). The vast majority admitted adoption of risky sexual behavior for syphilis acquisition (unprotected sex), while nearly half of them mentioned more than one sex partner during the previous months (Table 3).

Table 3. Demographics of syphilis infected patients in the general population in Greece

Characteristics of syphilis seropositive general population	2008, n (%)	2009, n (%)	2010, n (%)
Total tests	416	482	375
Positive tests	65 (15.6)	71 (14.7)	59 (15.7)
Gender			
Males	47 (70.3)	50 (70.0)	51 (86.5)
Females	18 (27.7)	21 (30.0)	8 (13.5)
Origin			
Greek	43 (66.2)	54 (76.5)	51 (86.5)
Immigrants	22 (33.8)	17 (23.9)	8 (13.5)
Way of transmission			
Heterosexual contact	35 (53.8)	38 (53.5)	12 (20.3)
Homosexual contact	22 (33.8)	23 (32.5)	24 (40.7)
Other/unknown	8 (12.4)	10 (14.0)	23 (38.9)
Age (years), mean $\pm$ standard deviation	44.1 $\pm$ 11.34	46.6 $\pm$ 8.31	45.1 $\pm$ 10.21
Symptomatic infection	34 (52.3)	44 (62.0)	35 (59.3)
Concurrent STDs	18 (52.9)	27 (61.3)	20 (57.1)
Multiple sex partners	33 (50.7)	32 (45.04)	26 (44.06)
Unprotected sex	58 (89.2)	52 (73.2)	49 (83.05)
Stage of infection			
Primary	21 (32.3)	25 (35.2)	22 (37.3)
Secondary	15 (23)	30 (42.3)	19 (32.3)
Latent	29 (44.6)	14 (19.7)	16 (27.0)
Neurosyphilis	1 (1.5)	2 (2.8)	2 (3.4)

Male gender and patient age did not correlate with the incidence of syphilis in the general population. On the other hand, origin from a country other than Greece (HR 4.6, 95%CI: 1.1-18.5, $p=0.005$), and homosexual contact (HR 3.1, 95%CI 0.8-9.7, $p=0.003$), both were individual risk factors for syphilis in the general population. Additionally, as well as in the HIV population, high risk sexual behaviors such as history of multiple sex partners (HR 8.1, 95%CI: 2.8-26.2) and unprotected sex predicted syphilis infection (HR 7.9, 95%CI: 2.6-25.2, overall $p<0.001$) [data not shown].

Discussion

The aim of this study was to identify the epidemiological traits of a syphilis outbreak among HIV patients in our geographic area compared to the simultaneous outbreak in the general population. This study was based on data from the Reference Center of HIV and Infectious Diseases of Northern Greece and the Reference Centre of General Population. It is the first time that such a study is performed in our country and we believe it may contribute beneficially to the enhancement of existing national infectious diseases surveillance systems, especially during the current refugee and economic crisis that Greece suffers.

Multiple sexual partners, unprotected sex, being on HAART and coinfection with other STDs were risk factors for acquiring syphilis in this epidemic in our HIV population. Declining trends in some countries may be due to alterations in healthcare systems, diagnostic tests and recording rather than real changes of the incidence.¹¹ In other countries, dramatic increases were noted and could probably be attributed (based on the male-to-female ratio) to the recent rise in syphilis among MSM.¹² A significantly greater proportion of patients with syphilis had a history of multiple sexual partners and did not use protective measures during sexual contact ($p<0.001$). The overall high rate of unprotected sex is probably attributed to HAART-related treatment optimism and reduced fear of transmitting STDs.¹⁸ In the HAART era, HIV infections continue to rise,¹⁹ which suggests that many seropositive patients

continue to engage in unprotected sexual intercourse post HIV diagnosis, leading to acquisition and transmission of additional STDs and exposure of their partners to infections. The coexistence of STDs has also been linked to multiple anonymous sex partners, lack of condom use, web use for meeting sex partners, and more widespread use of recreational drugs and sildenafil.¹⁴ Moreover, the lateral effect of highly active antiretroviral therapy (HAART) to augmented syphilis transmission rates among HIV-infected individuals has also been reported.¹⁵ HAART improves immunological status in the setting of HIV infection, which makes patients less vulnerable to other infections, and at the same time it leads to HIV RNA virological suppression. The latter reduces the possibility of HIV transmission to other individuals. This fact has been associated with risky sexual practices due to strong confidence and reassurance of patients on HAART for low risk of HIV transmission and other STDs and consequently the rejection of condom use.

The use of HAART has been associated with reduced HIV transmission in sero-discordant couples,^{20,21} it has been associated with decreased use of safe practices and STDs prevention measures. Serosorting is also an important issue raised from our study, in which a significant proportion (more than a quarter) of syphilis patients were sexual partners of syphilis infected adults, irrespectively of HIV status and derived from risky sexual practices. It is confirmed that coexistence of other STDs is a predisposing factor for transmitting other STDs.^{1-3,5} HAART administration is not a reason for closer management of these patients, except for the first three months of administration which is the necessary time period for detecting possible adverse events (renal, marrow toxicity, allergic reactions, jaundice) of HAART initiation. So we should not imply that HAART intake is associated with better surveillance of STDs or more frequent regular visits of HIV patients to healthcare services.

A change in sexual behavior with more risk-taking practices is likely to have contributed to the recent increase in STDs in Europe, making

the need for enhanced preventive actions urgent.²²

Our results highlight the increased rate of syphilis, especially among MSM and HIV-infected MSM. Among people living with HIV followed at the HIV reference center of Northern Greece, MSM seem to be the major risk group for acquiring new STDs. Moreover, most of these MSM were not newly diagnosed HIV patients. Therefore, clinician alertness intensified testing, prompt diagnosis, early treatment and contact tracing are essential measures in order to control a syphilis outbreak in an HIV population.

Our study is subject to certain limitations. First, by not discriminating separately each sexually transmitted infection, we may underestimate the full spectrum of STDs emerging among people living with HIV and the most risky one for acquiring syphilis.⁵ However, syphilis was chosen due to its sudden and increased incidence, comprising a moderate but still uncontrolled outbreak in the HIV population in Northern Greece. Second, our attempt to identify specific high-risk factors was limited by a significant proportion of missing data in our database. Missing data may be attributed to the discomfort in asking more personal information especially in the general population or to clinician time constraints. Third, no data are available on the role of social media applications to find partners in this study. Though, their use was not as wide during the outbreak as it currently is.

The rise of syphilis incidence in the general population during this period is remarkable. The population tested consisted of normal adults at high risk of acquiring an STD or having a symptomatic condition. To control testing bias we excluded HIV coinfecting persons and sex-workers from this population. Literature shows that increased frequency of testing increases syphilis detection. Moreover, symptomatic individuals are more likely to be syphilis positive. The most significant point is that MSM are the main source of recycling STDs including syphilis in the adult population, irrespectively of HIV status. This fact confirms high risk behaviors

among MSM, despite HAART intake and prevention campaigns.

The results of our study underline the importance of regular screening for STDs among HIV-positive people. Moreover, our findings show a need for improved sexual health promotion among MSM. Our study also suggests that the use of safe sexual practices to prevent STDs has decreased and it is important to emphasize the use of barrier methods also during oral sex, given that this is an usual route for syphilis transmission.²³ Further studies are needed to better understand the epidemiology of HIV/syphilis coinfection in MSM and most certainly HIV-positive individuals and immigrants should be a priority for STD prevention actions.^{6,24-26} Additionally, closer surveillance of the general population is needed even in high-income countries since the epidemiology of syphilis and other STDs may change throughout the years.²⁷

It is also worth mentioning that HIV patients in Northern Greece are described mainly as late presenters²⁸ (delayed HIV diagnosis) and in many cases, HIV diagnosis was simultaneous with syphilis diagnosis. This fact may justify the delayed stage of syphilis identified in coinfection cases (latent vs. secondary vs. primary syphilis). The classification of syphilis cases refers to the incidence of syphilis (new cases during 2008-2010), which was determined post completing the testing and diagnostic procedure for each patient (blood serology testing, lumbar puncture). Previous screening campaigns were also implemented before 2008, but the incident cases were fewer among HIV patients served in our Infectious Diseases Unit. Screening was intensified during 2009-2010 to assess the outbreak risk factors and to prevent expansion of the infection.

Conclusion

In summary, diagnosis of a sexually transmitted disease in an HIV patient is a crucial clinical event that should trigger the clinician's suspicion for high-risk sexual behavior.²⁹ Sexual health assessments should be a routine process for HIV patients during follow-up visits.³⁰ For high-risk patients, screening for STDs should be

done at least annually or more frequently as recommended by many experts.³⁰⁻³⁴ Our study also suggests that the use of protection methods against STDs has dropped and it is important to emphasize the specific use of barrier methods during oral sex, given that this is a route for syphilis transmission.²³

Further studies are needed to better understand the epidemiology of HIV/syphilis coinfection in MSM and definitely HIV-positive people and immigrants should be a priority for STD prevention actions.^{24,27,32-34} Even currently, syphilis remains a huge public health issue and this underlines the importance of adding further data to investigate risk factors.³⁵ Surveillance of STDs in AIDS Reference Centers could identify risk groups and detect different STDs emerging among the HIV population in a specific region. These data are useful for healthcare professionals, for the implementation of screening strategies and prevention efforts to reduce HIV transmission.¹⁶

Authors' contributions statement: OT contributed to the initial idea and design of the manuscript, the interpretation of data, drafting and revising the article, and approved the final version of the draft for publication. LS interpreted the laboratory results, contributed to the design of the study, edited the manuscript and approved its final version. EC contributed to the idea, concept and design of the manuscript, the analysis and interpretation of the data, drafting and revising of the article and approved the final version of the manuscript for publication. PK contributed to the design of the manuscript, drafting and revising of the manuscript, and approved the final version of the manuscript. ES performed the laboratory tests and contributed to the concept and design of the manuscript, the interpretation of data, drafting and revising the article, and approved the final version of the manuscript for publication. PZ contributed to the idea and design of the manuscript, the interpretation of data, drafting and revising the article, approved the final version of the manuscript and performed part of the statistical analysis. EV examined the participants, interpreted the results and contributed to the concept of the manuscript, revised the article, and approved the final version of the draft for publishing. AM performed the laboratory tests and wrote part of the manuscript, revised it and approved its final version. SM contributed to the organization of the study, performed statistical analysis, revised the manuscript and approved its final version. All authors read and approved the final version of the manuscript.

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