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Review Article

Effect of Levothyroxine Treatment on Heart Rate Variability in Hypothyroidism: Systematic Review and Meta-Analysis

Valentin Brusseau[1*], Igor Tauveron[2], Reza Bagheri[3], Ukadike Chris Ugbolue[4], Valentin Magnon[5], Valentin Navel[6], Jean-Baptiste Bouillon[7], Frederic Dutheil[7]

[1]Department of Endocrinology, Diabetology and Metabolic Diseases, University Hospital of Clermont–Ferrand, Clermont-Ferrand, 63000, France; [2]Department of Endocrinology, Diabetology and Metabolic Diseases, University Hospital of Clermont Auvergne, Clermont–Ferrand, F–63000, France; [3]Department of Exercise Physiology, University of Isfahan, Isfahan, Iran; [4]Department of Health and Life Sciences, University of Strathclyde, Glasgow, Scotland, UK; [5]Department of Physiology and Psychosocial Stress, University of Clermont Auvergne, Clermont–Ferrand, F–63000 France; [6]Department of Ophthalmology, University of Clermont Auvergne, Clermont-Ferrand F-63000, France; [7]Department of Physiological and Psychosocial Stress, University of Clermont Auvergne, Clermont-Ferrand F-63000, France

ABSTRACT

Introduction: We performed a systematic review and meta-analysis of the effect of levothyroxine treatment on Heart Rate Variability (HRV) in hypothyroidism. Indeed, abnormalities of HRV exist in hypothyroidism, but their reversibility after treatment remains contradictory.

Methods: We searched for articles related to HRV parameters in treated and untreated hypothyroidism in different databases (pubmed, cochrane, embase, and google scholar) until November 15, 2022. We performed a meta-analysis for each HRV parameter, stratified according to the degree of hypothyroidism: RR intervals (or Normal to Normal intervals-NN), SDNN (Standard Deviation of RR intervals), RMSSD (square root of the mean difference of successive RR intervals), pNN50 (percentage of RR interval with more than 50 ms of variation), Total Power (TP), LFnu (Low-Frequency normalized unit), HFnu (High-Frequency normalized unit), VLF (Very Low Frequency) and LF/HF ratio.

Results: We included 10 studies with a total of 269 untreated hypothyroid patients, 184 treated hypothyroid patients and 348 healthy controls. After treatment, there was an increase in SDNN (ES=0.72, 95% CI 0.27 to 1.16), RMSSD (1.37, 0.34 to 2.39), pNN50 (3.04, 1.29 to 4.79), and a decrease in LFnu (-1.26, -2.46 to -0.06) and LF/HF ratio (-0.78, -1.42 to -0.15) ($p<0.05$), without significant difference for RR intervals, TP and HFnu. However, abnormalities persisted after treatment compared to controls ($p<0.05$) with lower SDNN (-0.72, -1.22 to -0.23) and HFnu (-0.83, -1.46 to -0.21) and higher LF/HF (0.35, 0.11 to 0.59).

Conclusion: After treatment, there is an improvement in the parameters of the HRV, hence a beneficial effect of levothyroxine substitution, particularly for monitoring the evolution of cardiovascular morbidity. However, this reversibility of abnormalities remains partial.

Keywords: Thyroid; Biomarker; Autonomic nervous activity; Prevention; Public health; Levothyroxin; Hypothyroid treatment

Correspondence to: Valentin Brusseau, Department of Endocrinology Diabetology and Metabolic Diseases, University Hospital of Clermont-Ferrand, 63000, France, Tel: +33473751309; E-mail: vbrusseau@chu-clermontferrand.fr

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INTRODUCTION

Thyroid hormones play a fundamental role in the modulation of the cardiac autonomic nervous system, allowing maintaining the homeostasis of the cardiovascular system [1]. Hypothyroidism is characterized by a lack of production of thyroid hormones by the thyroid gland, affecting up to 10%-15% of elderly people, making it the most common endocrine disease [2]. If left undiagnosed or untreated, hypothyroidism may be associated with changes in autonomic regulation of the cardiovascular system leading to a significant risk of ventricular arrhythmias and sudden cardiac death [3-7]. Indication of levothyroxine therapy depends on the etiology and severity of the hypothyroidism, age and comorbidities. Nevertheless, it is accepted that hypothyroidism with a TSH above 10 mIU/L should be treated, regardless of age, because of its cardiac and neurocognitive complications. However, the indication for treatment remains controversial when TSH is below 10 mIU/L. We can wonder whether levothyroxine therapy would reduce the abnormalities of the autonomic nervous system and thus cardiovascular consequences. Heart Rate Variability (HRV) is the fluctuation of the heart rate over time between two consecutive beats. The study of HRV allows an approach to sympatho-vagal balance by detecting the activity of cardiac sympathetic and parasympathetic components. Reduced HRV is associated with an increased risk of cardiac mortality and an increased risk of ventricular arrhythmias. Results reporting the effect of levothyroxine treatment on HRV parameters in hypothyroidism remain contradictory, including total reversibility of autonomic disorders.

We aimed to conduct a systematic review and meta-analysis of the impact of levothyroxine treatment for hypothyroidism on HRV parameters. A secondary objective was to identify the most frequently reported predictors (age, sex, body mass index-BMI, thyroid function).

We conducted this meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, without the need for ethics approval as there was no human or animal experiment.

LITERATURE REVIEW

We searched the main article databases (pubmed, cochrane library, embase, google scholar) until November 15, 2022, with the following keywords: ("Hypothyroidism" or "hypothyroid") and ("Heart Rate Variability" or "HRV") for studies reporting the effect of hypothyroidism treatment on HRV parameters in hypothyroid patients. Our primary end point was the effect of levothyroxine treatment on HRV parameters in hypothyroid patients. We did not select studies based on year of publication, geographic origin, or language. In order to examine all studies done on the subject, two authors (V.B and R.B) performed bibliographic searches electronically but also manually by exploring the reference lists of all publications meeting the inclusion criteria. These same two authors also extracted data from the articles. In case of disagreement, a third author was solicited (F.D). We excluded animal studies, studies in children, studies dealing with another intervention in combination with levothyroxine treatment, conferences, congresses, seminars, and studies without HRV parameters in the frequency or time domains [8].

Data extraction

The primary end point analysed was the effect of levothyroxine treatment on HRV parameters in patients with untreated hypothyroidism. We chose to analyse HRV by the linear method because it is the traditionally accepted method in clinical research. This method consists of measuring the time and frequency domains of HRV. In the time domain, we analysed the RR intervals, their Standard Deviation (SDNN), the Root Mean Square difference of Successive RR intervals (RMSSD), and the percentage of adjacent NN intervals varying by >50 milliseconds (pNN50). The frequency domain consists of a range of frequencies by decomposing the RR interval using the Fast Fourier algorithm or autoregressive modeling: Total Power (TP), Low Frequency power (LF, 0.04 ± 0.15 Hz), High Frequency power (HF, 0.15 ± 0.4 Hz), Very Low Frequency power (VLF, 0.003 ± 0.04 Hz), and the ratio LF/HF. Power is the energy found in a frequency band. LFnu and HFnu are relative powers to compare HRV parameters between two patients. They are obtained by dividing LF or HF by the total power: LFnu=LF/(LF+HF) and HFnu=HF/(LF+HF). Parasympathetic activity is represented by HF power and HFnu and is associated with RMSSD and pNN50. LF power is associated with SDNN and represents both parasympathetic and sympathetic activity. LFnu focus on the control and balance of cardiac sympathetic behaviour. Concerning the VLF power band, the physiological mechanisms responsible for its activity are still poorly understood, but we know that it correlates with SDNN, and thus with sympathetic and parasympathetic activity. Sympatho-vagal balance is represented by the LF/HF ratio [9].

Regarding the secondary endpoints, several parameters were studied: Sociodemographic (age, sex), anthropometric (BMI), clinical (blood pressure, duration and etiology of hypothyroidism, duration of treatment by levothyroxine), biochemical (Thyroid Stimulating Hormone-TSH, free thyroxine-fT4, free triiodothyronine-fT3) and electrical (heart rate).

Quality of assessment

We used two scores to judge the quality of the included articles. The Scottish Intercollegiate Guidelines Network (SIGN) score is based on different evaluation grids depending on the type of study. It is divided into two sections: Study design (14 items) and overall assessment (3 items). There were 4 response options (yes, no, can't say, or not applicable). The second score used is the “Strengthening the Reporting of Observational studies in Epidemiology” (STROBE-32 items/sub items). By assigning one point per item or sub item, we calculated a percentage of a maximum score.

Statistical considerations

Statistical analysis was performed using Stata software (v16, StataCorp, College Station, US). The main parameters were represented by two types of variables, categorical and continuous, which were reported as number (%) and mean ± Standard Deviation (SD), respectively. Each HRV end point was subjected to random-effects meta-analyses (DerSimonian and Laird approach) by comparing patients with untreated

hypothyroidism to those with treated hypothyroidism. We determined an Effect Size (ES, Standardized Mean Differences-SMD) for each end point; this is a unit less measure. If the ES is centered on zero, it means that the HRV parameters do not differ between treated and untreated patients. A positive SE reflects a higher HRV in treated patients, with 0.8 being a large effect, 0.5 a moderate effect, and 0.2 a small effect. We stratified by TSH levels, above 10 mIU/L, less 10 mIU/L, and undefined if TSH level was unknown. The heterogeneity of the studies' results was examined according to three parameters: Forest plots, Confidence Intervals (CI), and I-squared (I^2) ranging from 0% to 100%. Study heterogeneity was considered high if the I^2 was >50%. To address potential publication bias, we examined the funnel plots of these meta-analyses and performed additional meta-analyses by excluding studies not evenly distributed around the base of the funnel. If the sample size was sufficient, we performed meta-regressions on the secondary end points (age, sex, blood pressure, BMI, duration of treatment, fT3, fT4, TSH). Results were expressed as regression coefficients and 95%CIs, and P values less than 0.05 were considered statistically significant [10].

LITERATURE REVIEW

We conducted this meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, without the need for ethics approval as there was no human or animal experiment.

RESULTS

Using the keywords ("hypothyroidism" or "hypothyroid") and ("Heart Rate Variability" or "HRV"), we found 863 articles, of which 10 articles were included after removal of duplicates and use of selection criteria.

The 10 included articles were written in English, published between 2000 and 2018, and compared HRV parameters before and after levothyroxine therapy in patients with hypothyroidism. Eight of the 10 studies were prospective the rest were cross-sectional. A total of 269 patients had untreated hypothyroidism, 184 had treated hypothyroidism, and 348 were healthy controls.

Regarding thyroid function, all articles addressed hypothyroidism and used levothyroxine treatment exclusively, but two studies did not report TSH level ("undefined") two articles studied patients with pre-treatment TSH<10 mIU/L1,14, and six studies studied patients with pre-treatment TSH >10 mIU/L.

Regarding HRV measurement, half of the studies used a 24 hours holter-ECG to determine HRV and the other half of the studies used a supine ECG. This recording was done in spontaneous breathing with normal daily activity in an ambulatory setting for all studies.

The main characteristics of the studies are listed in Table 1. The objectives and quality of the articles, inclusion and exclusion criteria, and population characteristics, characteristics of hypothyroidism, and HRV measurements and analysis are described in the supplementary material [11].

Table 1: Characteristics of included studies.

Study	Country	Design	Sub group	Intervention	Duration*	Healthy controls	Age, years	Sex, % men	Before treatment			After treatment			ECG min	HRV parameter
									n	fT4, pmol/L	TSH, mIU/L	n	fT4, pmol/L	TSH, mIU/L		
Ahmed 2010	Bangladesh	Cross-sectional	2 groups Untreated overt hypothyroidism	No intervention	-	Yes	38.0 ± 1.2	0%	30	5.1 ± 1.9	38.2 ± 30.5				5	TP, LF, HF, LF/HF
			Treated overt hypothyroidism by LT**	Two different groups	15.0 ± 3.0		39.0 ± 0.7		-	-	-	30	15.1 ± 3.9	2.0 ± 1.0		

Cacciatori 2000	Italy	Prospective	1 group Overt	Treatment by LT with restauration of euthyroidism	15.0 ± 3.0	Yes	52.1 ± 5.	0%	7	3.1 ± 0.4	55.5 ± 9.5	7	15.0 ± 0.3	1.6 ± 0.2	10	RR, TP, LF, HF, LF/HF
Celik 2011	Turkey	Prospective	1 group Subclinical or overt hypothyroidism	Treatment by LT	6.0 ± 0.0	Yes	-	-	28	-	7.5 ± 2.9	28	-	1.3 ± 0.8	1440	RR, SDNN, RMSSD
Chintala 2018	India	Prospective	1 group Overt	Treatment by LT	1.0 ± 0.0	No	28.7 ± 7.	0%	25	9.3 ± 2.7	112.6 ± 42.6	25	-	32 ± 20	10	RR, RMSSD, TP, LF, HF, LF/HF
Falcone 2014	Italy	Cross - sectional	2 groups Untreated subclinical hypothyroidism	No intervention – Two different groups	-	Yes	71 ± 13	23.6 0%	55	24.5 ± 9.0	5.4 ± 1.4	-	-	-	1440	RR, SDNN, RMSSD, pNN50
			Treated subclinical hypothyroidism by LT		unspecified		68 ± 13	18.7 0%	-	-	-	71	16.5 ± 5.7	2.1 ± 0.9		
Galetta 2006	Italy	Prospective	1 group Subclinical	Treatment by LT	6.0 ± 0.0	Yes	-	-	15	-	10.2 ± 3.0	15	-	1.9 ± 0.7	1440	RR, SDNN, RMSSD, pNN50, LF, HF, LF/HF
Galetta 2008	Italy	Prospective	1 group Overt	Treatment by LT	6.0 ± 0.0	Yes	54 ± 12	29%	31	0.7 ± 0.1	56.2 ± 14.7	31	-	2.2 ± 0.9	1440	RR, SDNN, RMSSD, pNN50, LF, HF, LF/HF

Guasti 2006	Italy	Prospective	1 group	Overt	Stop LT for 4 weeks, even LF therapy for 8 weeks	1.8 ± 0.3	No	-	-	42	2.6 ± 1.3	87.4 ± 22.0	42	22.1 ± 3.2	0.01 ± 1.0	15	RR, LF, HF, LF/HF
Heemstra 2010	The Nether lands	Prospective	1 group	Overt	Stop LT for 4 weeks, even LT therapy for 8 weeks	1.8 ± 0.0	Yes	46 ± 10	36.4 0%	11	1.4 ± 0.7	142. 4 ± 34.4	11	24.8 ± 4.1	0.8 ± 1.0	15	RR, LF, HF, VLF, LF/HF
Xing 2001	China	Prospective	1 group	Overt	Treatment by LT	3.0 ± 0.0	Yes	51 ± 13	-	18	-	71.0 ± 31.2	18	-	4.6 ± 2.1	1440	SDNN, RMSSD, pNN50, LF, HF, LF/HF

*Duration: Duration of treatment, months; **LT: Levothyroxine

FT4: Free Thyroxine; TSH: Thyroid-Stimulating Hormone; RR: RR intervals (or Normal-to-Normal intervals-NNs); SDNN: Standard Deviation of RR intervals; pNN50: percentage of adjacent NN intervals differing by more than 50 milliseconds; RMSSD: The square Root of the Mean Squared difference of Successive RR-intervals, TP: Total Power, LF: Low Frequency, HF: High Frequency, VLF: Very Low Frequency, LF/HF ratio: Low Frequency/High Frequency Ratio.

Effect of levothyroxine on HRV in hypothyroid patients

In comparison to untreated hypothyroid patients, treated hypothyroid patients had significantly higher SDNN (ES=0.72, 95% CI 0.27 to 1.16), RMSSD (1.37, 0.34 to 2.39), pNN50 (3.04, 1.29 to 4.79), HF power (1.30, 0.31 to 2.29) and lower LFnu (-1.26, -2.46 to -0.06) and LF/HF ratio (-0.78, -1.42 to -0.15). Other parameters were not significant. No meta-analysis was performed for VLF because only one study reported it [12].

Stratification by TSH levels

Treated hypothyroid patients with TSH above 10 mIU/L had significantly lower RR intervals (ES =-0.41, 95%CI -0.66 to -0.16), LFnu (-1.26, -2.46 to -0.06) and LF/HF ratio (-1.03, -1.84 to -0.23), and higher HF power (0.92, 0.21 to 1.65) compared with untreated patients ($p<0.05$). We found no significant difference in RMSSD, TP, LF power, and HFnu. Only one study measured SDNN and pNN50, showing a significant difference but without much interpretability for a meta-analysis. All meta-analyses had a high degree of heterogeneity (>50%), except studies investigating the RR intervals with low heterogeneity ($I^2<25\%$). Few or no studies addressed the effect of levothyroxine treatment on time or frequency-domain HRV parameters in hypothyroid patients with TSH below 10 mIU/L, precluding robust meta-analysis.

Treated patients compared with healthy controls

Some HRV parameter abnormalities persist in treated hypothyroid patients ($p<0.05$) with lower SDNN (-0.72, -1.22 to -0.23), LF power (-0.56, -1.09 to -0.02), HF power (-0.62, -1.19 to -0.04), and HFnu (-0.83, -1.46 to -0.21) and higher LF/HF (0.35,

0.11 to 0.59), without significant difference in other parameters (RR, RMSSD, pNN50, TP, LFnu).

Meta-regressions and sensitivity analyses

TSH levels were associated with lower TP (-0.06, -0.09 to -0.02) and HF power (-0.03, -0.06 to -0.01) ($p<0.05$). Duration of treatment by levothyroxine was associated with higher TP (0.30, 0.16 to 0.45), lower LFnu (-0.19, -0.38 to -0.01) and LF/HF ratio (-0.15, -0.27 to -0.04) ($p<0.05$). Men were associated with lower HFnu (coefficient= -6.66, 95% CI -12.7 to -0.58) and higher LF/HF ratio (5.08, 1.29 to 8.86) ($p<0.05$). No other significant results were observed for the variables age, BMI, blood pressure, fT4 and fT3 levels. No meta-regressions were possible for pNN50 parameter because of a lack of data from the different included articles. After excluding studies that were not distributed around the base of the funnel, we repeated the meta-analyses and the results remained similar (data not shown) [13].

DISCUSSION

The main results showed an increased HRV in patients with treated hypothyroidism compared untreated hypothyroidism that may be explained by a benefit of levothyroxine treatment on HRV parameters. The decrease sympathetic and increase parasympathetic activity may have clinical and therapeutic implications.

The results of this meta-analysis showed a partial reversibility of HRV in patients with treated hypothyroidism compared with untreated hypothyroidism, which may be explained by a benefit of levothyroxine treatment on HRV parameters. This decrease in HRV is explained by a decrease in sympathetic activity and an increase in parasympathetic activity that may have clinical, diagnostic, and therapeutic implications [14].

Effects of levothyroxine on HRV parameters in hypothyroidism

Thyroid hormones play a fundamental role in maintaining cardiovascular homeostasis by modulating the autonomic nervous system. Hypothyroidism is associated with an increase in sympathetic activity that might be explained by an increase in catecholamines. Similary, the decrease of parasympathetic activity in hypothyroidism may be linked with the decrease in the sensivitiy of muscarinergic receptors. A treatment is effective on HRV parameters when there is an improvement in the sympatho-vagal balance in favor of parasympathetic activity. This efficacy is expressed by an increase in HF, TP, and time domain values. In our meta-analysis, levothyroxine treatment in hypothyroidism allowed this improvement in HRV parameters, mainly due to an increase in cardiac parasympathetic activity, hence the decrease in the LF/HF ratio and the greater increase in HF compared with LF. Some studies have reported no difference in RR interval before and after treatment of hypothyroidism, which is the case in our meta-analysis. However, when we compare the parameters of treated hypothyroid patients with those of healthy controls, we can observe a persistence of parasympathetic inhibition despite the restoration of euthyroidism. There is thus a partial reversibility of the HRV abnormalities after levothyroxine treatment, which suggests a partially reversible part to these disorders. Indeed, we can assume that there are irreversible changes or adaptation of the autonomic nervous system after long-term exposure to hypothyroidism, as there are often diagnostic delays due to the aspecific nature of the symptoms. It is possible that the lack of complete reversibility is due to a too short duration of treatment, which would imply that the autonomic nervous system set point is restored at more than 6 months. Indeed, an increase in the duration of treatment is associated with increased TP and decreased LFnu and LF/HF, thus with an improvement in sympathovagal balance. TSH stimulates sympathetic production in the central nervous system, thus playing a key role in determining sympathovagal imbalance. According to our metaregressions, elevated TSH was associated with a decrease in TP and HF after treatment, suggesting persistence of HRV abnormalities despite treatment. The lack of data does not allow us to conclude on the efficacy of treatment on HRV parameters in hypothyroid patients with TSH below 10 mIU/L. We observed a smaller therapeutic response in men with decreased HFnu and increased LF/HF. We can therefore note that the reversibility of HRV abnormalities is less obvious in men, which can be explained by lower sympathetic activity and higher parasympathetic activity than women [15].

Clinical and therapeutic implications

There is a strong link between the cardiovascular system and thyroid hormones. Hypothyroidism will be associated with multiple cardiovascular system impairments, such as coronary artery disease, heart failure and cardiovascular mortality. Indeed, several studies have shown alteration of the cardiovascular system by small but persistent changes in TSH, including a higher risk of sudden death when TSH is increased. These cardiovascular changes may in part be explained by changes in the cardiac autonomic nervous system.

These data suggest that levothyroxine therapy would decrease the cardiovascular complications of hypothyroidism by reducing HRV abnormalities, benefiting patient health. Indeed, an increase in HRV indicates better neurovegetative control and better functionality of the cardiovascular system. Duration of treatment was associated with an increase in HRV, implying beneficial effects on cardiovascular risk after a few months of treatment. No conclusions can be drawn for hypothyroidism with TSH below 10 mIU/L due to lack of data. Cardiac abnormalities in hypothyroidism depend on the severity of the disease, but treatment could prevent progression to more severe hypothyroidism and long-term cardiovascular complications. For this purpose, an evaluation of HRV parameters after long-term treatment in hypothyroid patients with TSH below 10 mIU/L is necessary.

LIMITATIONS

Meta-analyses are subject to various kinds of bias, including bias in the individual studies that make up the analysis. Furthermore, we conducted the meta-analyses on only published articles, so they are theoretically exposed to publication bias [16-18]. However, the use of broader keywords in the search strategy limits the number of missing studies. The quality of the

studies varied despite our rigorous criteria for including studies in the meta-analysis. The monocentricity of the included studies limits the generalizability of our results [19]. In addition, the declarative data of the studies constitute a putative bias. The included studies were very heterogeneous, which could affect our results. This heterogeneity was found both in their design, inclusion and exclusion criteria, in the collection of data, and in the conditions for measuring HRV. We tried to limit this bias by excluding extreme results that were not distributed around the base of the funnel. We had limited data on the etiology and duration of hypothyroidism that did not allow us to conclude on these parameters. Were poorly reported, which prevented further analysis. Similarly, the lack of data in hypothyroid patients with TSH below 10 mIU/L did not allow us to conclude on the effect of levothyroxine therapy on HRV abnormalities in these patients. In perspective, the evaluation of long-term levothyroxine therapy, especially in mild hypothyroidism, needs further study. The reproducibility of HRV measurement may provide additional insight and facilitate patient management. For example, HRV could be used to assess the adequacy and efficacy of levothyroxine dosing [20].

CONCLUSION

We were able to report strong evidence of an overall increase in HRV in treated hypothyroid patients compared to untreated hypothyroid patients, without total reversibility of abnormalities. These effects may have clinical implications such as a reduction in cardiovascular complications. The benefits of HRV assessment in the monitoring of treatment of hypothyroidism should be further investigated, given its potential as a noninvasive, reliable, and pain-free measure.

DECLARATION OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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AUTHOR CONTRIBUTIONS

Conceptualization: Valentin Brusseau and Frederic Dutheil; Methodology: Valentin Brusseau, Igor Tauveron, Reza Bagheri, Ukadike Chris Ugbolue, Valentin Magnon, Jean-Baptiste Bouillon, Valentin Navel and Frederic Dutheil; Software: Valentin Brusseau, Igor Tauveron, Reza Bagheri, Ukadike Chris Ugbolue, Valentin Magnon, Jean-Baptiste Bouillon, Valentin Navel and Frederic Dutheil; Formal analysis: Valentin Brusseau, Igor Tauveron, Reza Bagheri, Ukadike Chris Ugbolue, Valentin Magnon, Jean-Baptiste Bouillon, Valentin Navel and Frederic Dutheil; Validation: Valentin Brusseau; Resources, Valentin Brusseau and Reza Bagheri; Data curation: Valentin Brusseau; Writing–original draft: Valentin Brusseau, Igor Tauveron and Frederic Dutheil; Writing–review AND editing: Valentin Brusseau, Igor Tauveron, Reza Bagheri, Ukadike Chris Ugbolue, Valentin Magnon, Jean-Baptiste Bouillon, Valentin Navel and Frederic Dutheil; Visualization, Valentin Brusseau and Frederic Dutheil; Supervision: Valentin Brusseau and Frederic Dutheil; Project administration: Valentin Brusseau, Igor Tauveron and Frederic Dutheil.

All authors have read and agreed to the published version of the manuscript.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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