INPLASY PROTOCOL

To cite: Ferdinand et al. Association between melatonin deficiency and progressive adolescent idiopathic scoliosis: protocol for a systematic review and meta-analysis. Inplasy protocol 202070083. doi: 10.37766/inplasy2020.7.0083

Received: 18 July 2020

Published: 18 July 2020

Corresponding author:
Nyankoue Mebouinz Ferdinand

fnnyankouemebouinz@yahoo.fr

Author Affiliation:
Department of orthopaedic and trauma surgery, University teaching Hospital Aristide Le Dantec, Cheikh Anta Diop University

Support: **None.**

Review Stage at time of this submission: **Formal screening of search results against eligibility criteria.**

Conflicts of interest: **None.**

Association between melatonin deficiency and progressive adolescent idiopathic scoliosis: protocol for a systematic review and meta-analysis

Ferdinand, NM[1]; Fabrice, AB[2]; Mazou, NT[3]; Valerie, NA[4].

Review question / Objective: **Is melatonin deficiency associated with a progression of idiopathic scoliosis in adolescents?**
Condition being studied: **Adolescent idiopathic scoliosis (AIS) is a three-dimensional deformation of the spine associating a lateral curvature with a vertebral rotation(Khouri et al., 2004). Globally, the prevalence of AIS among adolescents is estimated at 0.5 to 3% (Stirling et al., 1996). AIS is associated with a high treatment cost which poses a huge economic burden for patients and have a significant psychosocial and aesthetic impact on the adolescent's lifestyle (Charroin et al., 2014; Deceuninck et al., 2012). Several theories have been proposed to explain the pathophysiology. Among theses, melatonin deficiency has been recognized as one of the main factors involved in the development of scoliosis. It has been suggested that idiopathic scoliosis results from a postural disorder induced by a melatonin (De Sèze et al., 2012). Besides its role in the circadian cycle, melatonin has an antigonadotropic action. In children, it would prevent early sexual maturation and, thus, influence the time of onset of puberty ; the earlier the onset of puberty, the more severe and protracted will be the evolution of AIS (Duval-Beaupère et al., 1970). Epidemiological evidence have incriminated melatonin deficiency as a predictor of progression of spinal curvature in AIS(Machida et al.,2009). However, there is still controversy.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 18 July 2020 and was last updated on 18 July 2020 (registration number INPLASY202070083).

INTRODUCTION

Review question / Objective: **Is melatonin deficiency associated with a progression of idiopathic scoliosis in adolescents?**

Condition being studied: **Adolescent idiopathic scoliosis (AIS) is a three-dimensional deformation of the spine associating a lateral curvature with a vertebral rotation(Khouri et al., 2004). Globally, the prevalence of AIS among**

adolescents is estimated at 0.5 to 3% (Stirling et al., 1996). AIS is associated with a high treatment cost which poses a huge economic burden for patients and have a significant psychosocial and aesthetic impact on the adolescent's lifestyle (Charroin et al., 2014; Deceuninck et al., 2012). Several theories have been proposed to explain the pathophysiology. Among theses, melatonin deficiency has been recognized as one of the main factors involved in the development of scoliosis. It has been suggested that idiopathic scoliosis results from a postural disorder induced by a melatonin (De Sèze et al., 2012). Besides its role in the circadian cycle, melatonin has an antigonadotropic action. In children, it would prevent early sexual maturation and, thus, influence the time of onset of puberty ; the earlier the onset of puberty, the more severe and protracted will be the evolution of AIS (Duval-Beaupère et al., 1970). Epidemiological evidence have incriminated melatonin deficiency as a predictor of progression of spinal curvature in AIS(Machida et al.,2009). However, there is still controversy.

METHODS

Participant or population: All adolescent patients, with or without active scoliosis, in whom the melatonin assay was carried out. According to the WHO, individuals aged 10 – 20 years will be considered as adolescents.

Intervention: Not applicable.

Comparator: Not applicable.

Study designs to be included: Cross-sectional, cohort,and case-control studies with available data to assess the association between melatonin deficiency and the progression of AIS.

Eligibility criteria: All studies involving human subjects meeting the following criteria will be included: 1. Study design: cross-sectional, cohort, and nested case-control studies with available data to assess the association between melatonin deficiency and the progression of AIS 2. Study participants: All adolescent patients, with or without active scoliosis, in whom the melatonin assay was carried out. According to the WHO, individuals aged 10 – 20 years will be considered as adolescents. 3. Exposure: Melatonin deficiency will be the exposure of interest. This will be assessed as a dichotomous variable (Melatonin deficiency vs no deficiency). Melatonin deficiency will be defined as a plasma value below 80pg/ml at night and less than 10pg/ml during the day(Karasek et al., 2006).

Information sources: First, relevant summaries published on the relationship between melatonin deficiency and the progression of adolescent idiopathic scoliosis will be identified by searching the MEDLINE, EMBASE, Cochrane Library, and Global Health Library databases through Ovid® from January 1 1960 to April 2020 using keywords. Examples of key words used will include: melatonin, scoliosis. This search strategy will be adapted to suit other databases. The reference lists of eligible full-text articles and relevant reviews will be scrutinized to identify citations missed during our search. Authors of eligible articles will be contacted to request further information relevant to answer our review question, where necessary

Main outcome(s): A scoliosis will be said to be progressive if the lateral curvature of the spine, measured by the angle of Cobb, increases by at least 5 ° per year.

Data management: Two review authors (FNM, FAB) will use a pre-structured data abstraction form to independently collect information on the surname of the first author, country, year of publication, sample size, average or median age of study participants at diagnosis, proportion of females, mean or median nocturnal and diurnal melatonin concentration in both exposure groups, type of idiopathic scoliosis, initial Cobb angle, annual progression (annual variation of the Cobb angle), duration of follow-up, number of participants in each exposure group,

number of participants who developed the outcome, measures of relative risk (odds ratio, hazard ratio, risk ratio) and their standard errors or 95% confidence intervals for the association between melatonin and AIS, and variables adjusted for. Both authors will check each other's abstracted data for accuracy and errors. Any disagreement will be resolved by discussion, and a third investigator will be consulted to arbitrate unresolved disagreements.

Quality assessment / Risk of bias analysis: Two authors (FNM and FAB), will assess the risk of bias in studies eligible for this review using the Joanna Briggs scale (24). An additional file will show this scale in detail. Risk of bias assessment will be classified as high, moderate and low risk of bias. Where insufficient information is available to assess the risk of bias, the corresponding author or first author of the said study will be contacted to obtain the missing information. We will classify the risk of bias as uncertain if no feedback is received from the corresponding author or first author. The risk of selection bias will be assessed using the Cochrane Guidelines available in Review Manager V.5.3 (http://tech.cochrane.org/revman).

Strategy of data synthesis:
The data collected will be analyzed by VNA using Stata V.16 software (Stata Corp). The natural logarithm of the risk ratio (RR) and its variance for the association between melatonin deficiency (versus no melatonin deficiency) and AIS will be calculated for each study eligible for meta-analysis. The log RR for each study will be weighted using the inverse-variance weighted method. The pooled RR will be calculated using a fixed-effects meta-analysis model. Statistical heterogeneity will be assessed and quantified using the Cochrane Q Chi-square test and I2 statistic, respectively. I2 values of 25%, 50% and 75% will represent low, medium and high heterogeneity, respectively. In case of high heterogeneity, we will perform a subgroup analysis using the following grouping variables: sex, age group, quality of the study, topographic forms of scoliosis according to King's classification. Publication bias assessment will be assessed using funnel plots and Egger test. Sensitivity analysis will be conducted to evaluate the strength and significance of the association between melatonin deficiency and AIS using studies which adjusted for key confounders like age, gender, body mass index, stage of bone maturation according to Risser. In addition, sensitivity analysis will be conducted including only studies with low risk of bias.

Subgroup analysis: Not applicable

Sensibility analysis: If necessary, sensitivy analysis using standard will be performed.

Language: No restriction.

Country(ies) involved: Senegal, Cameroon, United Kingdom (UK).

Keywords: Melatonin, Idiopatic Scoliosis, Adolescents, Systematic review.

Contributions of each author:
Author 1 - Nyankoue Mebouinz Ferdinand - Conceived and designed the protocol, drafts the manuscript and revised successive drafts of manuscript. He is the guarantor of the review.
Author 2 - Arroye Betou Fabrice - Conceived and designed the protocol, drafts the manuscript and revised successive drafts of manuscript.
Author 3 - Mazou N Temgoua - Conceived and designed the protocol, drafts the manuscript and revised successive drafts of manuscript.
Author 4 - Ndip Agbor Valerie - Drafts the manuscript and revised successive drafts of manuscript.