World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(RESEARCH ARTICLE)

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Sickle cell disease and assessment of energy metabolism and serum cortisol in Lubumbashi

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World Journal of Advanced Research and Reviews, 2024, 22(03), 2082–2088

Publication history: Received on 18 May 2024; revised on 26 June 2024; accepted on 29 June 2024

Article DOI: https://doi.org/10.30574/wjarr.2024.22.3.1963

Abstract

Introduction*:* Sickle cell disease is an inherited red blood cells disorder which leads to oxidative stress and resulting in the disturbance of energy metabolism.

Objective*:* The aim of this study was to evaluate changes in serum glucose, triglycerides and cortisol concentrations in subjects with sickle cell disease in the city of Lubumbashi.

Methods*:* This is a 1-1 matched case-control study involving 64 subjects with sickle cell disease attending the sickle cell care center (C-fare) and 64 subjects without sickle cell disease taken as controls. The serum obtained after centrifugation of the blood, taken from each of them, was used for the determinations of glucose, triglycerides and cortisol. The average results obtained in sickle cell patients and non-sickle cell patients were statistically compared using the Student's t test.

Results: the mean serum values of glucose, triglycerides and cortisol observed in sickle cell patients are respectively 71.77 ± 10.03 mg/dl, 98.78 ± 57.34 mg/dl and 399.48 ± 194 .62 nmol/L. In control subjects, these values are 76.98 ± 12.29 mg/dl, 60.09 ± 29.86 mg/dl and 421.35 ± 178.74 nmol/L, respectively. Mean blood glucose is significantly lower ($p < 0.01$) while triglyceridemia is significantly higher ($p < 0.000001$) in sickle cell patients than in controls, while there is no significant difference (> 0.05) concerning cortisolemia between the groups.

Conclusion*:* This study shows that during sickle cell disease, there is disruption of energy metabolism with a decrease in blood sugar and an increase in triglyceridemia.

Keywords: SS anemia; Energy metabolism; Cortisol; Lubumbashi

1. Introduction

Sickle cell disease is the most common genetic disease worldwide (1), this is produced by the mutation in β-globin gene in which the 17th nucleotide is changed from thymine to adenine and the sixth amino acid in the β-globin chain turn into valine instead of glutamic acid (2-3). It is an autosomal recessive hemoglobinopathy (4-6) and constitutes a crucial public health problem worldwide (7,8). The disease affects more than 50 million people worldwide, particularly in sub-Saharan Africa and the Mediterranean region (9). Depending on global population growth, by 2050 this figure could increase (10) and the number of newborns with sickle cell disease may reach an estimated 14.24 million (11).

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In black Africa, the prevalence of this disease fluctuates between 10 and 40% (12) and the Democratic Republic of Congo (DRC) is widely affected with a prevalence which ranks as the second country in Africa, after Nigeria, the DRC is third in the world after India and Nigeria (13).

Mortality related to sickle cell disease represents approximately 9 to 16% among children under five years old in countries with high prevalence (14). The pathogenic mechanism in sickle cell disease is mainly due to chronic inflammation associated with oxidative stress (15). The physiological response to stress includes the activation of both the central nervous system, the endocrine and immune systems (16). More researchers focused their studies on the increase in cortisol levels in response to stress (17) but the hypothalamic-pituitary-adrenal axis plays a vital role in this phenomenon. Cortisol is the classic stress hormone at the peripheral level and is easy to measure. Its effects are directed towards acute energy supply, protection against excessive inflammation and improvement of the hemodynamic state (18, 19). Cortisol, the main glucocorticoid, is synthesized in the zona fasciculata of the human adrenal cortex, and its biological concentration reflects acute, chronic, and diurnal changes in physiological and psychological events (20). The cortisol awakening response refers to the sharp increase in cortisol levels observed immediately following awakening in order to increase the body energy production, to replenish and maintain glycogen stores as well as to meet the needs of the active state of the body (21). Thus, physiological and endocrine alterations induced by stress, disruptions of functional systems (ei clinical parameters), biochemical (e.g. hormones) and metabolic systems become inevitable resulting in alterations of metabolic biomarkers (metabolites, enzymes, hormones) (22).

The main objective of this study is to evaluate the modification in energy metabolism associated with sickle cell disease by determining blood sugar, triglyceridemia and cortisol.

2. Material and methods

2.1. Site of research

The C-Fare medical center was the site where blood samples were collected from sickle cell patients while the blood samples of the control group were collected at the laboratory of the University Teaching Hospital of Lubumbashi, this is where all the biochemical analysis were performed. Lubumbashi, the second largest city in the Democratic Republic of Congo (DRC), is the capital of Haut-Katanga province, which is located in the African Copperbelt (23).

2.2. Study Population

This study was conducted on 64 children with sickle cell anemia (Hb SS) with their age ranging from 1 and 23 years (mean age value of 10.20 ± 3.14 years) and 64 control group with their age fluctuating from 2 to 21 years (mean value age of 11.59 ± 4.14). The selection was made without distinction of race, tribe and social class.

The exclusion criteria were:

- Children who have not been diagnosed with homozygous sickle cell disease by hemoglobin electrophoresis and those who have been transfused in less than 3 months
- Children in a period of sickle cell crisis were also excluded.

The study was approved by the ethics committee of the University of Lubumbashi (Approval UNILU/CEM/100/2022 of June 3, 2022) and each participant signed the informed consent form.

2.3. Equipment used

- Spectrophotometer (Cyanstart),
- Finecare analyzer
- Centrifuge (Horizon),
- Water bath (Memmert),
- Fridge (Liebherr),
- Mixer (Cat rem 5) ,
- Micropipettes (Eppendorf),
- Bowls,
- Stopwatch,
- Tubes with red cap ,
- The BD Vacutainer system (needle, body and collection tube)

- Tourniquet,
- Wadding,
- Alcohol,
- Yellow and blue tips.

2.4. Specimen collection and handling

Four ml of venous blood were collected using sterile needles through gentle venipuncture after sterilization of puncture site by alcohol, and collected samples were put into test tubes without anticoagulant at the C-fare Medical Center for sickle cell subjects and at the University teaching hospital of Lubumbashi for control group. The blood samples collected at the C-fare Medical Center were immediately (the same day) sent to the University Teaching Hospital of Lubumbashi for analysis. The blood was centrifuged at 2500 rpm for ten minutes before any laboratory analysis.

2.5. Laboratory analyzes

2.5.1. Blood sugar measurement

Blood sugar levels were measured using a colorimetric and enzymatic glucose-oxidase method. The principle is as follows: Glucose is oxidized in aqueous solution, following the action of glucose-oxidase in gluconic acid and hydrogen peroxide (H_2O_2). In the presence of a chromogen (aminophenazone) and peroxidase, hydrogen peroxide is transformed into $2H_2O$ and the chromogen turns red. The intensity of the color formed is proportional to the serum glucose concentration (24).

Measurement of serum triglycerides

Triglycerides were measured using an enzymatic and colorimetric method. The principle is as follows: Triglycerides are enzymatically hydrolyzed by lipoprotein lipase (LPL) into glycerol and fatty acids. This glycerol reacts with glycerol kinase (GK). The resulting glycerol-3-phosphate is then transformed by glycerol-3-phosphate oxidase (GPO) releasing hydrogen peroxide (H_2O_2). The concentration of hydrogen peroxide is determined by the Trinder reaction, which results in the formation of a red colored derivative. The intensity of the color formed is proportional to the concentration

Cortisol dosage

The determination of blood cortisol was carried out by the Finecare™ Cortisol rapid quantitative test which is based on the fluorescence immunoassay technique. It uses a competitive immunodetection method. When the sample is added to the sample well of the test cartridge, the fluorescently labeled cortisol detector antibodies bind to the cortisol antigens in the blood sample and form immune complexes. As the complexes migrate onto the nitrocellulose matrix by capillary action, it cannot be captured by the cortisol antigens that have been immobilized on the test strip. But excess unbound fluorescently labeled cortisol-detecting antibodies are captured. Therefore, the more cortisol there is in the blood, the less unbound fluorescently labeled antibodies accumulate on the test strip. The signal intensity of cortisol-detecting antibodies reflects the amount of antigens and are processed in the FIA Finecare™ system to determine the concentration of cortisol in the blood.

2.6. Statistical analyzes

Statistical presentation and analysis of the present study was conducted using the mean values obtained from sickle cell disease subjects and controls. The comparison between the two groups were carried out using student t- test. The correlation coefficient was calculated to establish the possibility of a relationship between the different parameters. For all tests, $p< 0.05$ was considered statistically significant

3. Results

Analysis of this table shows that there is statistically a significant difference between controls and sickle cell patients with regard to blood glucose (76.98 **±** 12.29 vs 71.77 **±** 10.03 mg/dl, $P < 0.01$) and triglyceride (60.09 **±** 29.86 vs 98.78 **±** 57.34 mg/dl, $P < 0.00001$) while there is no statistically significant difference between the two groups regarding cortisol (421.35 **±** 178.74 vs 399.48 **±** 194.62 nmol/L, $P > 0.05$) and age (10.20 **±** 3.14 vs 11.59 **±** 4 .14 years, $P > 0.05$).

Table 1 Mean serum concentrations of glucose, triglycerides, and cortisol in sickle cell patients and non-sickle cell patients

	Witnesses	**Sickle cell patients**	**P=value**	**P=value**
Age	10.20 ± 3.14	11.59 ± 4.14	0.08730257	> 0.05
Blood sugar (mg/dl)	76.98 ± 12.29	71.77 ± 10.03	0.009559304	<0.01
Triglyceridemia (mg/dl)	60.09 ± 29.86	98.78 ± 57.34	4.65699E-06	< 0.000001
Cortisol (nmol/L)	421.35 ± 178.74	399.48 ± 194.62	0.510710891	> 0.05

Table 2 Distribution of sickle cell patients by sex

Sex	**Frequency**	**Percentage**
F	38	59,38%
M	26	40,63%
Total	64	100,00%

The table 2 shows a female predominance with a sex ratio of 1.46

4. Discussion

The present study showed a sex ratio (F/M) of 1.46 in SS patients, highlighting the predominance of female sex over the male sex. In our study these patients had no scientific justification because this disease is transmitted by the mode autosomal recessive. The majority of patients were young (mean age: 10.20 ± 3.14 years), as also found by Kengne et al. (mean age: (9.59 ± 7.14 years) in a study carried out at the Bafoussam Regional Hospital Center (RHB) on the relationship between haptoglobin polymorphism and the state of oxidative stress, the lipid profile and the cardiovascular risk in sickle cell patients in Cameroon in 2020 (25).

The main findings of this study was that sickle cells young people showed a statistically significant increase in serum triglyceride level ($p< 0.005$) compared to control subjects. This finding is consistent with the studies performed by other groups Akinbami et al., (2019) and Hama AH et al (2021) where the serum triglycerides level was statically higher in children with sickle cell anemia compared to the controls (26, 27). The hypertriglyceridemia found in these patients could be associated with the chronic inflammation (28) related to the increased production of endogenous VLDL lipids and the reduction in lipoprotein lipase activity due to oxidative stress (29).

Conversely, this study showed statistical reduction in serum glucose level in sickle cell patients compared to the control group ($p < 0.01$) probably due to a higher consumption of glucose by sickle cell red blood cells (HbSS). This increased consumption of glucose was not observed neither in subjects carrying the sickle cell trait (HbAS) nor in normal healthy individuals (HbAA) (30).

In addition, the hypoglycemia and hypertriglyceridemia found in this study may be related to genetic disruptions and to the physiopathology mechanism underlying the disease rather than this being associated to age, race, socioeconomic status or diet.

In this study, the mean value of serum cortisol level in sickle cell patients was lower than that found in control subjects, although not statistically significant ($p > 0.05$). This finding is in agreement with Hagag et al., (2015) who found significantly lower morning basal serum cortisol levels in sickle cell patients compared to the control group (32). In addition, Osifo et al. (1988) found that the average plasma cortisol levels in the AS and SS groups (during steady state) were within the normal range, but the average content of the SS group was significantly lower than that of the AA group (33) and Kölbel et al. (2022) found that people with sickle cell disease have lower morning cortisol compared to control group (21) in agreement with the finding in this study.

The study carried out in 2008 in Omani patients with major transfusion-dependent homozygous beta-thalassemia who consulted in the thalassemia clinic at the Royal Hospital showed that morning cortisol levels for all patients were in the normal range without suspicion of hypoadrenal cortical function (31).

Furthermore, el-Hazmi et al. (1992) found that patients with severe sickle cell disease had significant disturbances in cortisol levels compared to patients with mild disease with lower cortisol levels (34). The mean value in serum cortisol level was lower in sickle cell patients compared to the control group, but only 4.8% of these patients presented hypocorticism, because they had morning cortisol < 190 nmol/L (35). Moreover, Sobngwi et al. (2018) reported that relative adrenal insufficiency is not a rare event in sickle cell patients without crisis, although basal and post-stimulatory cortisol levels were normal, the incremental change in cortisol was significantly lower in the patients (6). Additionally, in the presence of sickle cell disease, th.E vast majority of participants failed to achieve a significant increase in basal cortisol level after stimulation.

5. Conclusion

The results of the present study on energy metabolism and variations in cortisol in subjects with sickle cell disease showed that the mean value of serum levels of glucose and cortisol were reduced while the mean value of triglycerides increased.

This study demonstrates that during SS anemia, there is an increase in glucose consumption and a reduction in the breakdown of triglycerides. Conversely, the reduction in cortisol production shown in this study may be associated with iron overload, oxidative stress, increased energy requirements and inhibition of lipoprotein lipase activity.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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