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Original Article

Hypogonadism in Type 2 Diabetic Patients at Bamako

Hypogonadisme chez les patients diabétiques de type 2 à Bamako

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ABSTRACT

Introduction. Diabetes is a chronic metabolic disease that can lead to severe hormonal disorders such as hypogonadism. The objective of our study was to better define the biological risk factors of infertility related to hypogonadism in type 2 diabetics. **Method**s. This was a retrospective descriptive and analytical cross-sectional study conducted at the Mali Hospital between January 2019 to August 2020. The markers being biologically monitored were: Testosteronemia, gonadotropins, prolactinemia, glycemia, glycated hemoglobin A1c. Results: This study included 55 patients with type 2 diabetes. The age group between 51-70 years was the most represented with 92.73% of the population, the young subjects were little represented. We found overweight and grade 1 obesity respectively in 29.09% and 5.45% of the diabetic patients in our study. Hyperglycemia and glycated hyperhemoglobin A1c were found in 92.73% and 78.18% of diabetic patients with significant differences P= 0.02 and P = 0.001 respectively. 65.45% of the men with type 2 diabetes had biological hypogonadism with testosterone concentrations below the normal value (≤ 2.2 ng/ml). 58.18% of these subjects reported a decreased sexual (P = 0.02). Conclusion: A high prevalence of hypogonadism was found in diabetic patients. Diabetes through its deleterious action on the blood vessel wall through oxidative stress and insulin resistance could promote or accelerate the development of hypogonadism.

RÉSUMÉ

Introduction. Le diabète est une maladie métabolique chronique pouvant conduire à des troubles hormonaux sévères comme l'hypogonadisme. Objectif : définir les facteurs de risque biologiques d'infertilité liés à l'hypogonadisme chez les diabétiques de type 2. **Méthode**s. C'était 'une étude rétrospective descriptive et analytique menée à l'hôpital du Mali entre janvier 2019 et août 2020. Les marqueurs suivis biologiquement étaient : La testostéronémie, les gonadotrophines, la prolactinémie, la glycémie, l'hémoglobine glyquée A1c. **Résultats** Cette étude a inclus 55 patients diabétiques de type 2. La tranche d'âge entre 51-70 ans était la plus représentée avec 92,73% des hommes diabétiques de type 2, les sujets jeunes étaient peu représentés. Nous avons retrouvé un surpoids et une obésité de grade 1 respectivement chez 29,09% et 5,45% des patients diabétiques de notre étude. L'hyperglycémie et l'hyperhémoglobine glyquée A1c ont été retrouvées chez 92,73% et 78,18% des patients diabétiques avec des différences significatives P= 0,02 et P = 0,001 respectivement. 65,45% des hommes diabétiques de type 2 présentaient un hypogonadisme biologique avec une concentration de testostérone inférieure à la valeur normale (≤ 2,2 ng/ml). 58,18% de ces sujets ont rapporté une diminution du désir sexuel (P = 0,02). **Conclusion**. Une prévalence élevée d'hypogonadisme a été trouvée chez les patients diabétiques. Le diabète, par son action délétère sur la paroi des vaisseaux sanguins à travers le stress oxydatif et la résistance à l'insuline, pourrait favoriser ou accélérer le développement de l'hypogonadisme.

INTRODUCTION

Diabetes is a metabolic disease that results in chronic hyperglycemia leading to severe and disabling micro- and macro-vascular complications. Epidemiological studies have reported that type 2 diabetes affects 90% of diabetic subjects. In Africa, nutritional habits and changing lifestyles, including overweight, obesity and sedentary lifestyles, may explain this epidemiological transition in developing countries (1,2). The majority of these diabetics are between 40 and 59 years of age and more than 175 million people with diabetes are estimated to be undiagnosed (3). Statistics from a hospital study in 2020 estimated the prevalence rate of type 2 diabetes in Mali to be 10.22% (4). These data could explain the incidence of risk factors for diabetes (5).

HIGHLIGHTS

What is already known on this topic
Diabetes can lead to other hormonal disorders such as hypogonadism.

What question this study addressed
The profile of biological markers of hypogonadism in type 2 diabetic patients at the Mali Hospital of Bamako.

What this study adds to our knowledge
About two third of type 2 diabetic patients have biological hypogonadism.

How this is relevant to practice, policy or further research.
To systematically search for an endocrine disorder even in the absence of sexual complaints in our patients with type 2 diabetes.

Hypogonadism is traditionally defined as the inability of the testis to produce testosterone at sufficient levels during the normal phases of testicular activation (6–8). Hypogonadism is responsible for functional and physical disorders related to a deficiency of testicular androgens (testosterone) and their active metabolites (9). This gonadotropic deficiency results in insufficient secretion of luteinizing hormone (LH) and follicle stimulating hormone (FSH), which affects testicular function (2,6) The diagnosis is most often easily made when there is a significant drop in total testosterone. In this case, FSH and LH measurements, together with testosterone and free testosterone, are the basic tests for the investigation of testicular function (6,10).

Male hypogonadism has been recognized at a high frequency in men with type 2 diabetes with low testosterone levels. In addition, numerous studies have shown that testosterone levels reported in men with diabetes are much lower than those in non-diabetics (11,12). These low testosterone levels have also been identified as reliable predictors of insulin resistance and the likelihood of developing type 2 diabetes (13). Thus, it has been confirmed that male patients with type 2 diabetes who have low total testosterone levels are significantly more likely to develop hypogonadism (14).

Hypogonadism associated with type 2 diabetes may exacerbate sexual dysfunction by reducing libido and further compromising vascular reactivity (15,16). The relationship between testosterone and type 2 diabetes is complex and probably mediated by obesity (17). Research on hypogonadism in diabetics remains underexplored in Mali, despite the sharp increase in the prevalence of this metabolic disease. The objective of our study was to better define in the Malian population, the biological risk factors of infertility related to hypogonadism in type 2 diabetics.

MATERIALS AND METHODS

Ethical aspects

The study was conducted in accordance with the ethical standards set out in the Declaration of Helsinki (1983). Inclusion in the study was carried out according to the rules of the legislation in force at the hospital in Mali and the strict respect of the confidentiality of the identity of the patients and their analysis results.

Type of study and participant

This was a retrospective study that took place in the Endocrinology Department and Laboratory of Mali Hospital. This study included 55 type 2 diabetic patients in the Endocrinology Department of Mali Hospital from January 2019 to August 2020. Eligible patients were selected according to the inclusion criteria set as follows: Type 2 diabetic male patient, presenting symptoms of hypogonadism of any age group, and availability of medical analysis results in the Endocrinology service and the Medical Biological Analysis Laboratory.

Collection of samples

Blood samples were taken in the morning after 12 hours of fasting in dry, EDTA and fluoride tubes for the determination of hormones, glycated hemoglobin A1c and blood glucose respectively in the biomedical analysis laboratory of the hospital in Mali. The tubes were immediately centrifuged at +4°C for 10 minutes at 3500 rpm and before recovery of serum and plasma.

Analytical approach

The kit used was designed specifically for the quantitative determination of testosterone, prolactin, LH and FSH in human serum. The test was performed with the MAGLUMI-800 Chemiluminescence Immunoassay Analyzer (CIIA). This instrument uses the chemiluminescence immunoassay (CLIA) sandwich method for the quantification of testosterone, prolactin, LH and FSH. The membrane-bound serum binds to anti-testosterone, anti-prolactin, anti-LH or anti-FSH monoclonal antibodies. Buffer and magnetic beads coated with another anti-testosterone, anti-prolactin, anti-LH or anti-FSH monoclonal antibody were carefully mixed and incubated at 37°C to form a sandwich reaction. The light signal was measured by a photomultiplier within 3 seconds as relative light units, which is proportional to the concentration of testosterone, prolactin, LH and FSH present in the sample. Calibration and quality control were the priority steps to verify and validate the analytical results. The reagents, calibrators and internal quality controls used for the testosterone assay were Testosterone (CLI, part number 130202010M), Prolactin (CLIA, part number 130202006M), LH (CLIA, part number 130202002M) and FSH (CLIA, part number: 130202001M) reagents, supplied by Shenzhen new industries biomedical engineering Co. in Mali.

Blood glucose was measured with the glucose oxidase enzymatic method according to the principle of Beer Lambert's law applied on the spectrophotometer at a wavelength λ= 505 nm. In this enzymatic reaction, glycose oxidase catalyzes the conversion of glucose to gluconic acid and H2 O2 (hydrogen peroxide), the hydrogen peroxide under the action of peroxidase, reduces a chromogen to give a red color, the intensity of which is proportional to the concentration of glucose in the serum. The capillary's HbA1c kit for the separation and quantification of the glycated HBA1c fraction of human blood by capillary electrophoresis in basic medium (pH: 9.4) on the capillary's 2 flex-piercing instrument was used. capillary's 2 flex-piercing is an automated instrument that allows to perform all the electrophoresis

sequences up to the obtaining of the hemoglobin profile for the quantitative analysis of the HbA1c fraction. The hemoglobin, separated in fused silica capillaries, are detected directly at a cell on the capillary by absorbance spectrophotometry at 415 nm, the specific absorption wavelength of hemoglobin.

Variables explored in the study

Socio-demographic data (age, gender and sexual desire questionnaire).

The biological parameters measured were: biological abnormalities of hypogonadism included testosterone (Te: 2.2-10.5 ng/mL), prolactin (PL: 5-15 ng/ml, LH (1.1-25 mUI/ml) and FSH (1.5-11.8 mUI/ml) levels.

An HbA1c level ≥ 6.5% (11.1 mmol/L) quantified according to methods calibrated to international references. This parameter reflects the average blood glucose level of the last three months of normal value between 3.8 - 6.1 mmol/L.

Hypogonadism was defined biochemically as testosterone < 2.2 nmol/L (18). In men, it is characterized by a reduction in one or both of the primary functions of the testes: sperm production and testosterone production (6)**.** These abnormalities may result from disease of the testis (primary hypergonadotropic hypogonadism) or from damage to the pituitary gland or hypothalamus (secondary hypogonadotropic hypogonadism). The distinction between these two conditions can be made by measuring serum luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels. Subjects with hypergonadotropic hypogonadism have high LH and/or FSH levels. In contrast, subjects with hypogonadotropic hypogonadism have decreased or normal LH and/or FSH levels that are inappropriate for the decreased testosterone concentration.

Univariate statistical analysis

The non-parametric Mann-Whitney-Wilcoxon test was used to compare the means of quantitative variables while χ 2 tests or Fisher's exact test, depending on the numbers, were used for qualitative variables. Differences were considered significant if the *probability (p)* of the observed difference under the null hypothesis was $p \leq 0.05$.

RESULTS

Socio-demographic characteristics of patients:

The age group between 51-70 years was the most represented with 65.45% of the population, young subjects were poorly represented with 20% in the 30-50 years age group. We found overweight and grade 1 obesity respectively in 29.09% and 5.45% of the diabetic patients in our study, and normal weight was found in 36 diabetic patients (65.45%). Hyperglycemia was reported in 92.73% of the diabetic patients and normal blood glucose was found in 5.45% of the study population with a significant difference P= 0.02. LH, FSH and Prolactin markers determined in conjunction with testosterone were all of normal concentration for the majority of type 2 diabetic patients.

Glycated hyperhemoglobin A1c was reported in 78.18% of our diabetic patients with a significant difference in the study population P = 0.001.

Prevalence of hypogonadism

A prevalence of biological hypogonadism was found in 65.45% of type 2 diabetic patients with a reduced testosterone level but the statistical difference was not significant *P = 0.46.*

Metabolic disorders predisposing to hypogonadism in type 2 diabetic patients

A disturbance of sexual desire was observed in 89.09% of our study population. This decrease was more marked in patients with hypotestosteronemia (58.18%), and we also observe that the difference between the decrease in sexual desire and testosterone was significant (P = 0.02).

Hyperglycemia and hypotestosteronemia were noted in 61.81% of our diabetic patients, which explains the relationship between hypogonadism and glycoregulation disorders because this disturbance of sexual desire linked to the drop in testosteronemia was more marked in the glycemia levels. high.

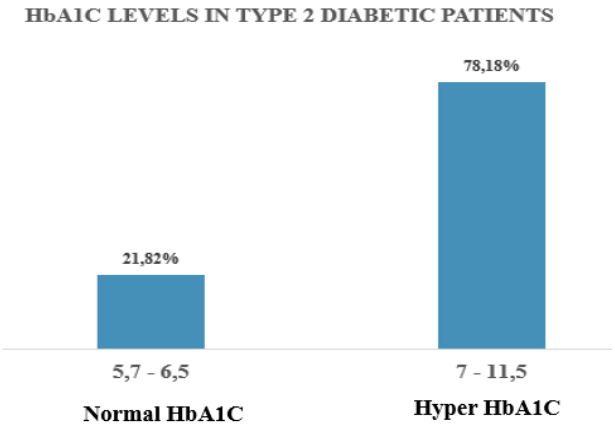

Figure 1: HBA1c levels in the study Type 2 diabetic patients.

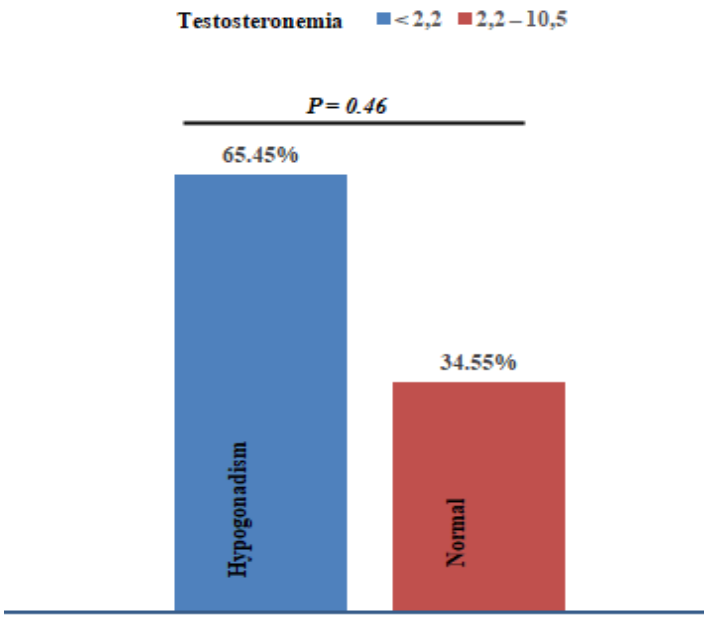

Figure 2: Distribution of testosterone levels in the study population.

Table I: Distribution of the population studied according to sexual desire.

Diabetic patients	Decreased sexual desire			*P*
Testosterone (ng/ml)	Non (%)	Oui (%)	Total	
< 2.2	4 (7.27)	32 (58.18)	36 (65.45)	***0.02***
2.2 – 10.5	2 (3.63)	17 (30.91)	19 (34.54)	
Total	6 (10.90)	49 (89.09)	55 (100)	

Table II: Evolution of the testosteronemia level according to the glycaemia

	Testosteronemia (ng/ml)			*P*
Glycaemia (mmol/L)	< 2.2	2.2 -10.5	Total	
< 3.8	1 (1.81%)	0	1 (1.8%)	*0.81*
3.8 – 6.1	1 (1.81%)	2 (3.64%)	3 (5.45%)	
> 6.1	34 (61.81%)	17 (30.91%)	51 (92.72%)	
Total	36 (65.43%)	19 (34.55%)	55 (100%)	

Table III: Testosterone levels according to HBA1c

	Testosterone (ng/ml)			*P*
HBA1c %	< 2.2	2.2 – 10.5	Total	
0 – 6.5	0	1(1.81%)	1(1.81%)	*0.18*
> 6.5	36 (65.45%)	18 (32.72%)	54 (98.19%)	
Total	36 (65.45%)	19 (34.55%)	55 (100%)	

The relationship between testosterone and HbA1c is inversely proportional because a decrease in testosterone is accompanied by an increase in HbA1c in 65.45% of the number of type 2 diabetic patients. This hypogonadism was more pronounced in patients whose testosterone levels were lower compared to patients whose testosterone levels were restored to normal either 32.72%.

Hypogonadism was observed in 45.45% and 20% of type 2 diabetic patients with normal BMI and overweight respectively. No statistically significant difference (P = 0.40) between serum testosterone and body mass index. We observe a lack of correlation between BMI and Testosterone (R^2: 0.0091).

Table IV: Distribution of testosterone level according to BMI

	Testosterone (ng/ml)			*P*
BMI (Kg/m²)	< 2.2	2.2 - 10,5	Total	
18 – 24.9	45.45%	18.18%	63.63%	*0.40*
24.9 -35	20%	16.36%	36.36%	
Total	65.45%	34.54	100%	

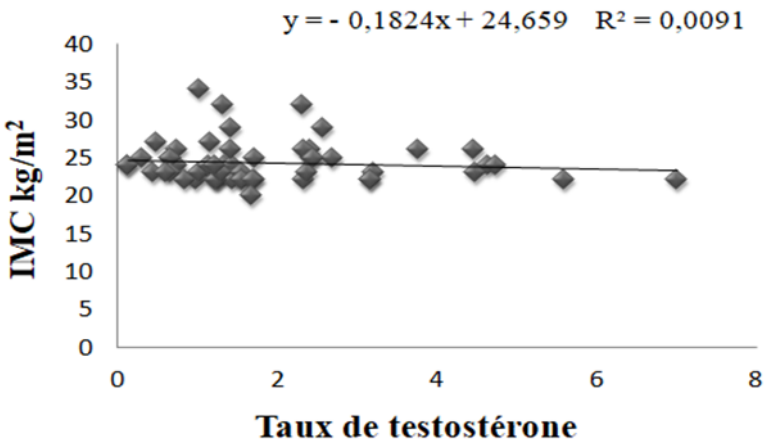

Figure 3: Relationship between testosterone level and BMI.

DISCUSSION

We conducted a study on the prevalence of hypogonadism in type 2 diabetic subjects in Mali, which involved 55 men on whom we performed testosterone, gonadotropins and prolactin assays, alongside blood glucose and HBA1C. In this study 65.45% of the men with type 2 diabetes had biological hypogonadism with testosterone concentrations below the normal value (Testosterone level ≤ 2.2 ng/ml). Most of these subjects reported sexual disorders such as decreased sexual desire with 58.18% (Table I) showing a significant difference P = 0.02. The age range of the recruited subjects was 30-80 years with a high representation of the age range 51-70 years. Hypogonadism is known to occur in about 4% of men aged between 40 and 70 years in one study (19), and has been reported in up to 65.45% of our age-matched diabetic population. Patients with type 2 diabetes have lower levels of free testosterone fraction than healthy men, with a higher incidence of hypogonadism. More severe testosterone deficiency symptoms were associated with lower quality of life scores in men with type 2 diabetes (20).

The determination of markers of hypogonadism in men with type 2 diabetes showed a disturbance of androgen and gonadotropin metabolism. In this study, the majority of men with type 2 diabetes had a 65.45% prevalence of biological hypogonadism with lower-than-normal testosterone concentrations (figure 2) but did not report a significant difference P = 0.46. Hypogonadism and erectile dysfunction have emerged as predictors of cardiovascular disease and may respond to lifestyle changes recommended for patients with diabetes and the metabolic syndrome (21). Studies have reported in the literature that up to one third of type 2 diabetic men over 18 years of age have low free testosterone and gonadotropin levels (18). Indeed, high and/or normal concentrations of the gonadotropin hormones LH and FSH would provide further support for the androgen metabolism disorders in our study. However, concentrations of LH, FSH and prolactin were found to be normal in all diabetic subjects in this study. Therefore, it has been shown that LH and FSH concentrations increase with age (22) and plasma testosterone levels were frequently lower in males with pathologies related to insulin resistance, which is much more common in our diabetic patients than in a population of the same age without any pathology (11,23). The results of these same studies suggest that a low plasma testosterone level may be associated with a higher risk of developing type 2 diabetes. On the other hand, authors have suggested that low plasma testosterone levels may be a predictive marker for the development of diabetes (24,25) and normal gonadotropin and prolactin concentrations in this context are more difficult to explain and deserve further exploration.

Obesity and low plasma testosterone levels are interdependent and strongly influenced by dietary factors, and their imbalances could lead to an elevated risk of hypogonadism (26,27). However, Tajar A et al (28) have shown that age does not contribute to increased secondary hypogonadism but that obesity and diet are strong inducers of hypogonadism. Thus, sex steroids are essential regulators of both reproductive function and energy metabolism, while their imbalance causes infertility, obesity, glucose intolerance, dyslipidemia. The literature (29) informs us that dietary restriction and weight control can improve the metabolic and reproductive outcomes of sex hormone-related conditions, including testosterone deficiency in men. The incidence of type 2 diabetes is

higher in the sedentary obese patient and this morbid association leads to an increased prevalence of hypogonadism (30). This high proportion of glycemic imbalance (HbA1C) found in 78.18% of our diabetic patients with a significant difference (P = 0.001) and 45.45% of obesity associated with biological hypogonadism in our study was much higher than previously reported by (26) or in other white or Arab populations (31,32). Indeed, the increasing urbanization in Africa is accompanied by profound changes in lifestyle, diet and lifestyle which tend to favor overweight and insulin resistance (33).

Hyperglycemia reported at 92.73% was correlated with hypotestosteronemia found in 61.81% of our diabetic patients. Recent studies (34,35) agree that there is a clear correlation between low testosterone levels and an increased incidence of cardiovascular disease, especially in cases where this decrease in testosterone triggered the vicious circle leading to the inflammatory metabolic syndrome, which was characterized by insulin resistance and a poor lipid profile. We found no correlation between testosterone and HbA1c levels, which is contrary to the analysis of another study which found that HbA1c has a statically non-significant tendency to be higher in hypogonadal subjects(36). The same study states that low testosterone levels in healthy men were associated with a high risk of developing insulin resistance and hormone supplementation reported in one study (37) may improve some markers of metabolic syndrome but also of glycemic control in type 2 diabetic patients.

CONCLUSION

This study therefore highlights the importance of comprehensive management of patients with type 2 diabetes. The concept of a higher prevalence of hypogonadism among diabetics in the African population is beginning to emerge. The explanation for this association remains complex. Whatever the mechanism, the presence of this dietary imbalance, obesity and hormonal disorders would potentiate the risk of hypogonadism associated with type 2 diabetes and all these risk factors are potentially modifiable and should be part of the diabetes management and prevention strategy in Africa. Given the large number of diabetic men with hypogonadism and sexual dysfunction, it would be appropriate to systematically search for an endocrine disorder even in the absence of sexual complaints in our patients with type 2 diabetes.

Conflicts of interest

The authors declare no conflict of interest.

Authors' contributions

All authors participated in the study either clinically or biologically, in the statistical analysis and in the writing.

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