

Evaluation of **non enzymatic status in** antioxidant capital in Senegalese type 2 diabetics.

ABSTRACT

Oxidative stress appears very early in the history of type 2 diabetes complications. It is associated to glucose oxidation but also to lipid peroxidation. This stress can be accentuated by a decrease in the antioxidant capacities in diabetics, especially if there are other comorbidities. The objective of this study was to evaluate the antioxidant capacity of Senegalese type 2 diabetics and to identify the associated risk factors.

We conducted a prospective study in 40 persons with type 2 diabetes. Factors related to age, sex, BMI, and BP were determined. For biological parameters, we measured blood glucose at empty stomach, glycated haemoglobin, total cholesterol, HDL, triglycerides and LDL, urea and creatinine, uric acid, albumin, total bilirubin, copper, and zinc.

The mean age of the population was 58 ± 11.24 years with a predominance of subjects aged over 60 (52.5%). The sex ratio was 1.11 with 52.5% male. Antioxidant capital was reduced in 60% of patients, with a predominance of women (35%). This reduction was marked by hypoalbuminemia (32.5%), hypozincemia (22.5) and an increase in the Cu/Zn ratio (30%). A strong correlation was found between the Cu/Zn ratio and total cholesterol ($r=0.911$; $p<0.0001$) as well as LDL ($r=1$; $p=0.0001$). Dyslipidaemia was found to be the most associated comorbidity with decreased oxidative capacity with an RR of 1.4 (CI=0.79-2.35) for total hypercholesterolemia and an RR of 1.6 (CI=0.75-3.71) for hypertriglyceridemia.

The antioxidant capital is reduced in type 2 diabetics, especially in dyslipidaemia conditions. Hygienic dietary measures and supplementation with trace elements such as zinc should prevent the complications of oxidative stress in diabetics.

Key words: Type 2 diabetes; Oxidative stress; Antioxidants; Comorbidities; Senegalese.

Introduction

Diabetes mellitus is a chronic hyperglycaemia related to absolute or relative insulin deficiency, often in conjunction with genetic and/or environmental factors. It is a chronic condition and is now considered a global health problem[1] . It is an arduous metabolic condition because of its mostly insidious course. It can expose patients to chronic degenerative complications but also to acute complications that can be life threatening [2], [3].

In diabetes mellitus, a state of oxidative stress is described by an imbalance between reactive oxygen species (ROS) and antioxidant defenses. [4]. This oxidative stress may be involved in tissue damage [5] and represent a potential risk factor for cardiovascular disease in type 2 diabetes. The decline in antioxidant defences is revealed by the determination of enzymatic and non-enzymatic antioxidants [6], [7]. Indeed, a decrease in enzymatic systems is mainly found with superoxide dismutase (Cu, Zn-SOD), Mn-SOD, catalase, extracellular SOD, and glutathione peroxidase (GSH-Px) [7]. Superoxide dismutase activity, which is the first line of defence against oxidative stress, is decreased in diabetes mellitus, especially in the case of zinc deficiency [8]. A Cu/Zn ratio of less than 1.5 is seen as an excellent marker of an individual's oxidative stress status [8]. In addition to the enzymatic defence systems, there is a non-enzymatic defence system that involves vitamins (C and E), albumin, uric acid, especially in its ionised form, bilirubin, and polyphenols [7], [8]. The aim of this study was to assess the antioxidant capital of diabetics and to identify the comorbidities associated with a reduction in this capital.

Methodology

This was a cross-sectional, and analytical study of diabetic patients followed at Principal Hospital (HPD) and Aristide le Dantec Hospital (HALD) in Dakar. All participants included in the study signed a consent form.

The data on age, sex, blood pressure (BP), weight, height, were collected during routine medical visits. Biochemical tests were performed using the Biosystem® A25 semi-automat with reagents from the same manufacturer except for Zinc, Copper (Spectrum, Egypt) and glycated haemoglobin (Human, Germany). Glucose, urea, total cholesterol, and its HDL fraction, uric acid and triglycerides were determined by enzymatic method. Total bilirubin was determined by colorimetric method as well as HbA1C, albumin, copper, zinc, and creatinine. Glomerular filtration rate (GFR) was obtained using the modified MDRD formula ($eDFG = 175 \times (Scr \times 0.0113)^{-1.154} \times age^{-0.203} \times 0.742$ (if female) $\times 1.212$ (if black)) and LDL-cholesterol using the Friedewald formula ($LDL-C$ (g/l) = Total cholesterol - (HDL-C - Triglycerides/5)). The non-enzymatic antioxidant capital was assessed by a decrease in uricemia, zincemia, albuminemia, bilirubinaemia as well as an increase in cupremia and/or the Cu/Zn ratio. Dyslipidaemia was retained according to NCEP III recommendations [9].

Statistical analysis was performed using SPSS V.26 software. Sociodemographic variables were expressed as a percentage. Chi-square tests of independence were used to test statistical associations. Spearman's correlation test was performed to seek associations between quantitative variables. The results of the tests were considered significant at p-values < 0.05.

Results

A total of 40 patients with type 2 diabetes (T2D) were included in the study. The mean age of the population was 58 ± 11.24 years with extremes of 32 and 78 years (Table 2). The most represented age group was over 60 years (52.5%) followed by

the group aged between 46 and 60 (27.5%) (Figure 1). The sex ratio was 1.11 with 52.5% male.

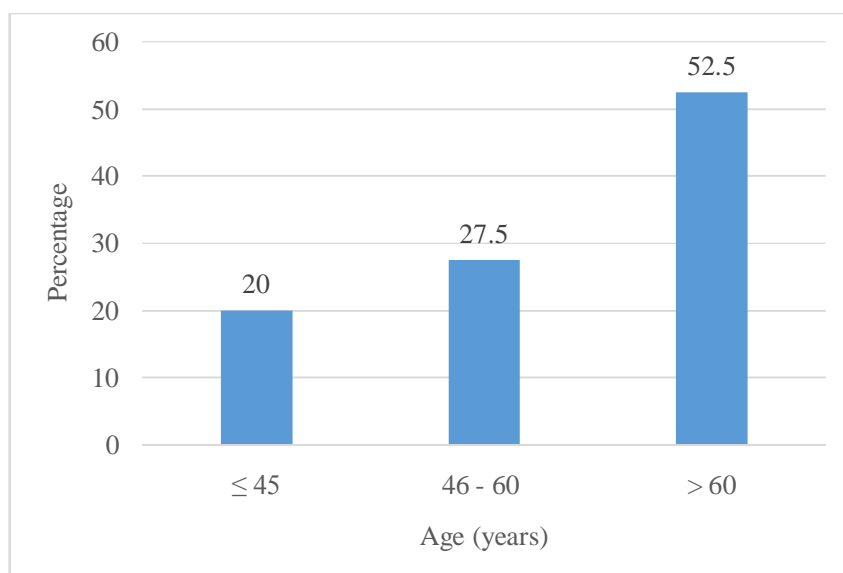


Figure 1 : Population distribution per age

The FRCV study showed overweight in 32.5% of subjects (n=13). Hypertension and dyslipidaemia were found in 42.5% (n=17) and 52.5% (n=21) of patients respectively. Impaired renal function was predominant in stage 2 CKD (n=16. 40%) followed by stage 3A (n=12. 30%) (Table 1).

Table 1 : FRCV distribution among the population.

		Nb of diabetics	Percentage	Total effective
BMI (Kg/m ²)	< 18	2	5	40
	18-25	23	57.5	
	25-30	13	32.5	
	> 30	2	5	
BP	Yes	17	42.5	
	No	23	57.5	
GFR (stages)	1	9	22.5	
	2	16	40	
	3A	12	30	
	3B	2	5	
	4	1	2.5	
Dyslipidaemia	5	0	0	
	Yes	21	52.5	
	No	19	47.5	

BP: Blood Pressure; BMI: Body Mass Index; GFR: Glomerular Filtration **Rate**.

The mean values of biochemical parameters were all within normal range except for blood glucose, which mean value was 1.67 ± 0.77 g/L (Table 2). Furthermore, diabetes was disordered in 5 patients (12.5%). Renal function was disturbed by elevated uraemia and creatininaemia in 14 (35%) and 16 (40%) patients respectively. Dyslipidaemia was found in 52.5% of subjects with an increase in total cholesterol (45%) followed by an increase in LDL (27.5%).

Table 2: Distributions of mean values of the study parameters.

Variables	Mean \pm SD (Min-Max)	References Values
Age (Years)	58 \pm 11.24 (32-78)	-
BMI (kg/m ²)	24.39 \pm 4.27 (17.4 - 41.1)	18 - 25
SBP (mm Hg)	122.75 \pm 11.98 (110 - 150)	120 – 140
TAD (mm Hg)	80.50 \pm 6.39 (70 - 90)	80 – 90
Glucose (g/l)	1.67 \pm 0.77 (0.96 - 4.31))	0.7 – 1.10
HBA1C (%)	5.87 \pm 1.13 (4.31 - 9.2)	< 6.5
Urea (mg/l)	0.47 \pm 0.32 (0.19 - 2.3)	0.15 – 0.45
Creatinine (mg/l)	12.21 \pm 5.03 (5.4 - 37.4)	< 13
GFR	73.4 \pm 25.7 (19.1 - 158.8)	> 90
Uric acid (mg/l)	54.43 \pm 12.88 (22.9 - 83.9)	35 – 72
Albumin (g/l)	36.20 \pm 4.14 (28 - 48)	35 - 50
Total cholesterol (g/l)	1.83 \pm 0.42 (1.1 - 2.8)	< 2
HDL (g/l)	0.54 \pm 0.11 (0.35 - 0.79)	H > 0.4 ; F > 0.5
Triglycerides (g/l)	1.22 \pm 0.42 (0.6 - 2.4)	< 1.5
LDL (g/l)	1.05 \pm 0.38 (0.26 - 1.98)	< 1.3
Zinc (μ g/l)	94.20 \pm 34.07 (23.7 - 177.8)	72 - 127
Copper (μ g/l)	1.05 \pm 0.18 (0.8 - 1.6)	H : 0.5 – 1.4 ; F : 0.8 – 1.55
Cu/Zn	1.30 \pm 0.67 (0.7 - 4.1))	< 1,5
Total bilirubin (mg/l)	4.93 \pm 2.17 (1.8 - 10.3)	\leq 10

SD: Standard deviation; BMI: Body Mass Index, SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure, HBA1C: Glycated Haemoglobin; GFR: Glomerular Filtration Rate; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein.

The study of antioxidant capital showed a decreased capital in 24 patients (60%) with a predominance of hypoalbuminemia (n=13, 32.5%) followed by an increased Cu/Zn ratio (n=12, 30%) (Table 3).

Table 3: Distribution of antioxidant capital in the population.

Parameters		Number	Percentage	Total effective
Albumin (g/l)	< 35	13	32.5	40
	≥ 35	27	67.5	
Uric Acid (mg/l)	< 35	2	5	
	≥ 35	38	95	
Copper (µg/l)	< 0.7	0	0	
	0.7 – 1.55	39	97.5	
	> 1.55	1	2.5	
Zinc (µg/l)	< 72	9	22.5	
	72 – 127	25	62.5	
	> 127	6	15	
Cu/Zn	< 1.5	28	70	
	≥ 1.5	12	30	
Total bilirubin (mg/l)	< 10	39	97.5	
	≥ 10	1	2.5	
HDL (g/l)	< 0.4	3	7.5	
	≥ 0.4	37	92.5	
Decrease in antioxidant capital	Yes	24	60	
	No	16	40	

The bivariate analysis (Table 4) showed a slight positive correlation of uricemia and blood pressure values TAS ($r=0.362$; $p<0.05$) and TAD ($r=-0.331$; $p<0.05$). A negative correlation was found between albumin and BMI ($r=-0.416$; $p=0.002$) but also with glycated haemoglobin ($r=-0.360$; $p=0.022$). A strong positive correlation of the zinc level was found with total cholesterol ($r=0.911$; $p<0.0001$) and LDL ($r=1$; $p<0.0001$). The Cu/Zn ratio was negatively correlated with changes in total cholesterol ($r=-0.863$; $p<0.0001$) and LDL ($r=-0.884$; $p<0.0001$). No correlation was found between carbohydrate parameters and antioxidant markers except between Cu/Zn ratio and HBA1C with $r=0.359$ ($p=0.023$).

Table 4: Correlation table of antioxidant capital parameters.

Parameters	AU		ALB		Zn		Cu		Cu/Zn		BILIT	
	r	p	r	p	r	p	r	p	r	p	r	p
AGE	0.07	0.677	-0.16	0.33	-0.05	0.743	-0.06	0.735	0.07	0.67	0.2	0.224
BMI	0.3	0.06	-0.48	0.002	0.25	0.128	0.19	0.25	-0.14	0.396	0	0.994
SBP	0.36*	0.022	-0.14	0.386	-0.03	0.88	-0.1	0.551	0.06	0.708	0.09	0.598
DBP	0.33*	0.037	-0.03	0.869	-0.15	0.366	-0.02	0.902	0.15	0.368	-0.01	0.968
Glucose	-0.14	0.39	0.11	0.5	0.05	0.77	0.01	0.95	-0.09	0.563	-0.04	0.813
HBA1C	0.11	0.5	-0.36	0.022	-0.22	0.167	0.23	0.146	0.36	0.023	0.17	0.297
Urea	0.25	0.121	-0.11	0.49	-0.15	0.366	0.08	0.641	0.17	0.298	0.09	0.577
Creatinine	0.15	0.345	-0.03	0.838	0.01	0.977	-0.09	0.592	0	0.996	0.18	0.274
GFR	-0.15	0.354	0.19	0.238	-0.06	0.738	-0.07	0.686	0.01	0.952	-0.16	0.339
CT	-0.07	0.686	0.19	0.232	0.91	<0.0001	0.19	0.24	-0.86	<0.0001	-0.23	0.147
HDL	-0.3	0.057	0.17	0.31	0.03	0.852	-0.25	0.115	-0.2	0.211	-0.22	0.178
TG	0.1	0.548	0.21	0.193	0.28	0.086	0.21	0.186	-0.24	0.136	-0.22	0.165
LDL	-0.01	0.962	0.09	0.598	1	<0.0001	0.26	0.1	-0.88	<0.0001	-0.13	0.415

BMI: Body Mass Index, SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure, HBA1C: Glycated Haemoglobin; GFR: Glomerular Filtration Rate; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein. CT: Cholesterol total; TG: Triglycerides; AU: Uric acid; ALB: Albumin; BILIT: Total Bilirubin.

Without finding a statistically significant difference ($p>0.05$), the decrease in antioxidant capital was predominant in males (RR=1.55 (CI=0.92 - 2.61)) and in patients with dyslipidaemia, especially in those with total hypercholesterolaemia (RR(CI)=1.4 (0.79 - 2.35)) and hypertriglyceridemia (RR(CI)=1.67 (0.75 - 3.71)). High blood pressure, increased BMI and impaired renal function did not appear to be involved in the decrease of antioxidant capital in our cohorts of diabetics (Table 5).

Table 5: Contingency table of antioxidant capital according to the parameters studied

Parameters		Decrease in antioxidant capital		RR	IC (95)
		No (%)	Yes (%)		
Sex	Female	5 (12,5)	14 (35)	1.55	0.92 - 2.61
	Male	11 (27,5)	10 (25)		
HBP	No	9 (22,5)	14 (35)	1.04	0.62 - 1.73
	Yes	7 (17,5)	10 (25)		
HBA1C (%)	≤ 7	15 (37,5)	20 (50)	0.71	0.42 – 1.21
	> 7	1 (2,5)	4 (10)		
BMI	< 25	11 (27,5)	14 (35)	0.84	0.51 – 1.38
	≥ 25	5 (12,5)	10 (25)		
GFR	≥ 60	12 (30)	13 (32,5)	0.71	0.44 – 1.15
	< 60	4 (10)	11 (27,5)		
Dyslipidaemia	No	7 (17,5)	12 (30)	1.11	0.67 - 1.83
	Yes	9 (22,5)	12 (30)		
↑ CT	No	7 (17,5)	15 (35,5)	1.4	0.79 – 2.35
	Yes	9 (22,5)	9 (22,5)		
↓ HDL	No	15 (37,5)	22 (55)	0.89	0.38 – 2.07
	Yes	1 (2,5)	2 (5)		
↑ TG	No	10 (25)	20 (50)	1.67	0.75 – 3.71
	Yes	6 (15)	4 (10)		
↑ LDL	No	11 (27,5)	18 (45)	1.14	0.62 – 2.09
	Yes	5 (12,5)	6 (15)		

HBP: High Blood Pressure; HBA1C: Glycated haemoglobin; BMI: Body Mass Index; GFR: Glomerular Filtration Rate; CT: Cholesterol total; HDL, High Density Lipoprotein; TG: Triglycerides; LDL: Low Density Lipoprotein.

Discussion

Several studies have focused on oxidative stress during diabetes mellitus and its implication in vascular complications [10], [11]. The aim of our study was to evaluate the antioxidant capital in Senegalese type 2 diabetic subjects. Our population consisted of 40 diabetic patients with a mean age of 58±11.24 years with extremes of 32 and 78 years. The most represented age group was over 60 years old (52.5%) followed by the group between 46 and 60 years old with 27.5%. The sex ratio was 1.11 with 52.5% of males. The mean values of the biochemical parameters were all within normal range except for blood glucose, which mean value was 1.67±0.77 g/L. Antioxidant capital was decreased in more than half of our population (n=24; 60%) with a predominance of hypoalbuminemia (n=13; 32.5%) followed by an increase in the Cu/Zn ratio (n=12; 30%). The decrease in antioxidant capital in diabetics has been reported by other authors. The work of Sow DS. *et al* in a Malian population showed an increase in enzymatic defence systems with an increase in superoxide

dismutase (SOD) (73.3%) [12]. Indeed, SOD is the first antioxidant fighting enzyme and its increase indicates oxidative stress and an antioxidant defence reaction [12]. Unlike SOD, glutathione peroxidase (GPX) levels were within normal limits in 97% of diabetics [12]. Other authors have reported lowered values [13], [14]. In this Malian case control study, the authors reported normal uric acid values in both populations and elevated total bilirubin values in 13% of diabetics [12]. These results are consistent with our study as the majority of our population had normal uric acid values (95%) and only one had an increased total bilirubin value (2.5%).

Hypoalbuminemia in our cohort of diabetic patients is reported by Dramé et al [15] with mean values slightly lower than in our study (36.2 vs 32.32 g/l). This hypoalbuminemia could aggravate oxidative stress, whatever its cause: decrease due to insufficient intake or protein leakage of renal origin [16]. The increase in plasma proteins and their glycation would play an important role in reducing oxidative stress by reducing the amplification of red cell oxidation [16].

To assess the enzymatic antioxidant capacity of our patients, we measured the cofactors of these enzymes, namely copper (Cu) and zinc (Zn) ions, and we also determined the Cu/Zn ratio. As a result, the increase in the Cu/Zn ratio is an excellent marker of the oxidative stress state of an individual [8]. In our study this ratio was elevated in 30% of diabetics (n=12) with a strong correlation in patients with high LDL (r= -0.884; p=0.0001) and increased total cholesterol (TC) (r= -0.863; p=0.0001). The increase in TC and LDL was also correlated with zinc levels with correlations of (r= 0.911; p=0.0001) and (r= 1; p<0.00001) respectively. Indeed, a decrease in blood zinc levels was found in 22.5% of our patients (n=9). This decrease in blood zinc levels was found by Omri et al [17]. In the study by Sobczak et al, a significant difference was found between diabetics and controls for serum zinc and cupremia with slightly lower values in type 2 diabetics [18].

In Bjørklund's review, the authors report the involvement of zinc in the regulation of insulin receptor expression. It prolongs the biological activity of insulin and appears to promote a healthy lipid profile [6].

The evaluation of comorbidities showed a predominance of dyslipidaemias (n=21; 52.5) with especially increased total cholesterol (n=45%) followed by hypertension (n=17; 42.5%) and stage 2 chronic kidney disease (n=15, 40%). Only patients with lipid disturbances had a slightly higher risk of having a decreased antioxidant capital. Lipid metabolism disturbances are important in diabetics with a profile varying according to the population, most often predominated by hypertriglyceridemia [19], [20]. Lipid oxidation could be mitigated by the action of HDL which unfortunately is most often decreased in diabetics [21], [22].

In their work, Kabamba et al [21] reported the role played by HDL in antioxidant defence, which was reduced in diabetics. This decrease would indicate a high level of circulating cholesterol and therefore a high exposure to free radicals [21]. This decrease in HDL was not significantly found in our study (n=3; 7.5%) unlike the increase in TC (n=18; 45%), triglycerides (n=10, 25%) and LDL (n=11; 27.5%).

In future studies, we intend to determine the activity of antioxidant enzymes to confirm this decrease in the antioxidant capacity of Senegalese type 2 diabetic patients.

Conclusion

Antioxidant capital is reduced in Senegalese type 2 diabetics presenting dyslipidaemia. A healthy dietary measure with zinc and protein supplementation should improve the quality of treatment and prevent the development of vascular complications.

Ethical Approval:

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

Consent

As per international standard or university standard, Participants' written consent has been collected and preserved by the author(s).

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