Scientific Research Publishing

World Journal of Cardiovascular Diseases, 2023, 13, 879-889
https://www.scirp.org/journal/wjcd
ISSN Online: 2164-5337
ISSN Print: 2164-5329

Assessment of Diabetes Control Level and Associated Cardiovascular Risk Factors

Désiré Alain Affangla[1,2*], Fabrice Doupa[1], Jean-Michel Amath Dione[1,2], Stéphanie Claudia Akanni[1,2], Hugues Elie Elame Ngwa[1,2], Djibril Marie Ba[1], Mohamed Cor Ben Omar Leye[1]

[1]Department of Medicine and Medical Specialties, Training and Research Unit of Health Sciences, Iba Der Thiam University, Thies, Senegal
[2]DIABCARMET Department, Saint Jean de Dieu Hospital, Thies, Senegal
Email: *docalaf@gmail.com

How to cite this paper: Affangla, D.A., Doupa, F., Dione, J.-M.A., Akanni, S.C., Ngwa, H.E.E., Ba, D.M. and Leye, M.C.B.O. (2023) Assessment of Diabetes Control Level and Associated Cardiovascular Risk Factors. *World Journal of Cardiovascular Diseases*, **13**, 879-889.
https://doi.org/10.4236/wjcd.2023.1312076

Received: November 29, 2023
Accepted: December 25, 2023
Published: December 28, 2023

Copyright © 2023 by author(s) and Scientific Research Publishing Inc.
This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).
http://creativecommons.org/licenses/by/4.0/

Open Access

Abstract

Introduction: Cardiovascular diseases are the leading cause of mortality in type 2 diabetics patients. Our work aimed to assess the level of control of type 2 diabetes and associated cardiovascular risk factors. **Patients and study method:** This was an observational cross-sectional study of type 2 diabetics patients. The parameters studied were: sociodemographic data, lifestyle, anthropometric data, levels of control of diabetes by the level of HbA1C, blood pressure measured at the office and cholesterol. **Results:** 326 type 2 diabetics patients were collected. The sex-ratio was 0.35. The average age of the patients was 58 ± 11 years. A physical inactivity remained present in 79 patients (24.23%), 2 patients (0.61%) continued to smoke. The prevalence of obesity was 21.16% (n = 69) or 25% of women and 10.4% of men (p = 0.01). Abdominal obesity was observed in 151 patients (46.31%), 139 of whom were female and 12 male (p = 0.001). Diabetes was sufficiently controlled in 65.34% of patients (n = 213) while cholesterolemia and hypertension were controlled in 33.44% and 8.33% of patients respectively. **Conclusion:** Type 2 diabetes was frequently associated with other cardiovascular risk factors. Control of diabetes and these factors was insufficient. Therapeutic education of type 2 diabetics patients needed to be improved.

Keywords

Control, Cardiovascular Risk Factor, Type 2 Diabetes, Senegal

1. Introduction

According to WHO, 24 million adults live with diabetes in Africa and this figure

is expected to rise by 129% to 55 million by 2045. The age-standardized mortality rate for diabetes is 48 per 100.000 inhabitants. This is more than double the global rate of 23 per 100.000. The first cause of death of the diabetic subject is represented cardiovascular diseases [1].

Our work aimed to assess the level of control of diabetes and associated cardiovascular risk factors.

2. Patients and Method

This was an observational cross-sectional study, conducted from April 13th, 2021 to July 07th, 2021 at the Diabetes and Cardio-Metabolic Diseases Management Centre (DIABCARMET). The patients are managed by specialist doctors, diabetologists and cardiologists.

2.1. Inclusion Criteria

Included in this study were T2D patients:

- 18 years of age or older;
- seen in external consultation;
- followed for at least 03 months at the DIABCARMET centre;
- having a patient record containing parameters to control cardiovascular risk factors.

2.2. Exclusion Criteria

Not included in this study were patients:

- type 1 diabetics;
- hospitalized type 2 diabetics;
- type 2 diabetics followed for less than three months at the DIABCARMET centre;
- whose files were incomplete;
- not having agreed to take part in this study.

2.3. Data Collection

The purpose and approach of our study was clearly explained to patients in order to obtain their consent. A standardized survey sheet in the form of a 6-page questionnaire was designed to collect the various data from our study. This questionnaire examined the following parameters:

❖ Socio-demographic data

- civil status: surname, first name, age, sex;
- the level of education in French: primary, secondary or university;
- the sector of activity according to the classification of the National Agency of Statistics and Demography of Senegal in sectors of primary, secondary and tertiary activity [2];
- Monthly income level: based on World Bank criteria of July 1st, 2020 [3];
- the type of health cover: mutual health insurance, health insurance or if he

pays at his own expense or with the help of a third party;

❖ Personal history

- the duration of the T2D;
- ongoing treatment and adherence;
- the duration of evolution of the other risk factors and their treatment;

❖ lifestyle, namely, active smoking, alcohol consumption and physical inactivity. Physical inactivity was selected for absence of daily physical activity or moderate intensity physical activity < 150 minutes or < 75 minutes for high intensity activity per week [4];

❖ Anthropomorphic data: weight, height, body mass index (BMI) by Quetelet index (weight/height^2 in kg/m^2), abdominal perimeter. Obesity was selected for BMI ≥ 30 kg/m^2; Abdominal obesity from a waist circumference ≥ 102 cm in men and 88 cm in women [5];

❖ the measurement of blood pressure in mm Hg at the office by an automatic blood pressure monitor OMRON Intellisense M6 Comfort. The normal value was a PAS < 140 and/or PAD < 90 mm Hg according to WHO [6];

❖ Comprehensive clinical review of all devices and systems;

❖ The biological paraclinical exploration included:

- Glycated hemoglobin with a normal rate < 6.5% [7];
- Total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides (g/l); the standards selected are those of ESC and EASD 2019 [7].

The objectives for controlling diabetes and cardiovascular risk factors were:

- a cessation of smoking;
- the absence of a physical inactivity;
- the absence of obesity with a BMI < 30 kg/m^2 and a waist circumference <102 cm in men and <88 cm in women;
- Glycated hemoglobin < 7% according to IDF [8];
- systolic blood pressure < 130 mm Hg and diastolic blood pressure < 80 mm Hg, according to French National Authority for Health [7];
- cholesterolemia as recommended by ESC and EASD in 2019 [7]:
  - Total cholesterol < 2 g/l;
  - HDL-c > 0.4 g/l;
  - A triglyceride level < 1.5 g/l;
  - LDL-c < 1 g/l; in patients with moderate CV risk; less than 0.7 g/l in patients with high CV risk and less than 0.55 g/l in patients with very high CV risk.

Patients with type 2 diabetes who had been at high cardiovascular risk for more than 10 years and/or with target organ involvement or cardiovascular disease or kidney failure were considered to be at very high risk.

2.4. Data Analysis

The data analysis was performed with the Excel 2010 software of the Microsoft office suite. The varied uni analysis made it possible to determine the distribu-

tion of each variable to be studied.

Quantitative data were expressed as a standard mean ± deviation.

The statistical test used was Xi^2 (Khi-two). It was considered significant for a p value < 0.05.

2.5. Ethical Considerations

The subjects investigated all gave their informed consent. The collection of their data was carried out in the respect of anonymity with confidentiality of the information provided.

3. Results

Of a total of 404 patients surveyed, 326 met the inclusion criteria of our study. The number of patients not included was 78 (19.3%). The reasons for exclusion were represented by incomplete patient records (93.59%), a follow-up time of less than three months (5.13%), type 1 diabetes (1.28%). No patient refused to participate in the investigation.

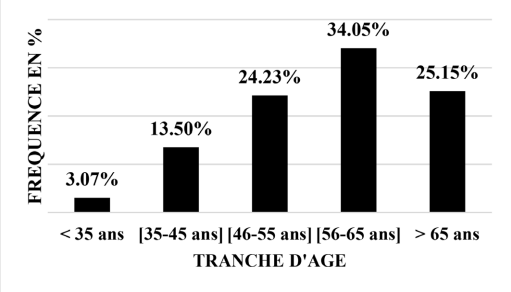
3.1. Sociodemographic Data

The average age of patients was 58 ± 11 years (extremes of 23 and 90 years). The age group [56 - 65] was the most represented with 111 patients (34.05%), followed by those over 65 with 82 patients (25.15%) (**Figure 1**). 240 female (74%) and 86 male (26%) diabetics; a gender ratio of 0.35.

The proportion of subjects enrolled in the French language was 61% (n = 200 patients), 41% at an elementary level, 37% at a secondary level and 22% at the university level.

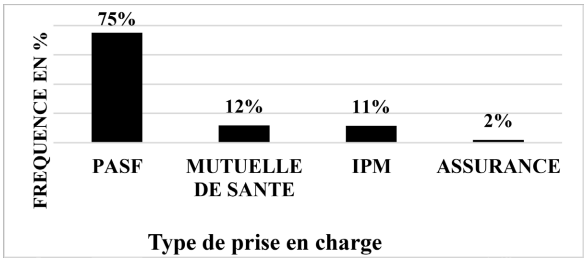
One hundred and eighty-two patients (55.8%) were unemployed or retired. Among those who had a profession, the tertiary sector was most represented with 119 patients (36.5%) of the population. Middle-income patients were most represented with 49% in the lower middle and 44% in the upper middle.

The majority of patients (75%) did not have health coverage and paid for their care and medication. The others were either affiliated with a health insurance company or were covered by the Institute of Health Insurance or insurance as shown in **Figure 2**.



Ans: years; Fréquence: frequency; Tranche d'âge: age group.

Figure 1. Age distribution of patients.



PASF (PAE): Paid at own expense; Mutuelle de santé: Mutual health insurance; IPM (HII): Health Insurance Institute; Assurance: insurance; Type de prise en charge: Type of medical care.

Figure 2. Distribution of patients by type of medical care assistance.

3.2. Lifestyle

Seventy-nine patients remained sedentary (24.23%) including 64 women and 15 men ($p = 0.10$). A notion of smoking was found in 4 patients (1.23%), 2 of whom had stopped smoking for less than 3 years. Alcohol consumption was found in 19 patients (5.83%); including 7 women and 12 men ($p = 0.001$).

3.3. Duration of Development of Diabetes

Patients with a duration of diabetes of more than 10 years were the most represented ($n = 128$; 39.26%), followed by those with 1 to 5 years of diabetes with ($n = 115$; 35.28%).

3.4. Anti-Diabetic Treatment

The most prescribed therapeutic protocols for patients were the combination biguanides-sulfamides hypoglycemic to 96 patients (29.45%) followed by the combination Biganide-Insulin and Biguanide alone prescribed to 51 patients each (15.64%) (**Table 1**).

3.5. Adherence to Anti-Diabetic Treatment

In our study, 184 patients (56.44%) had minimal adherence problems, 99 patients (30.37%) had good adherence, and 43 patients (13.19%) had poor adherence (**Figure 3**). Adherence was significantly related to the monthly income level ($p = 0.05$) but was not related to the education level ($p = 0.50$) and the professional sector of the patients ($p = 0.50$).

3.6. Diabetes Control

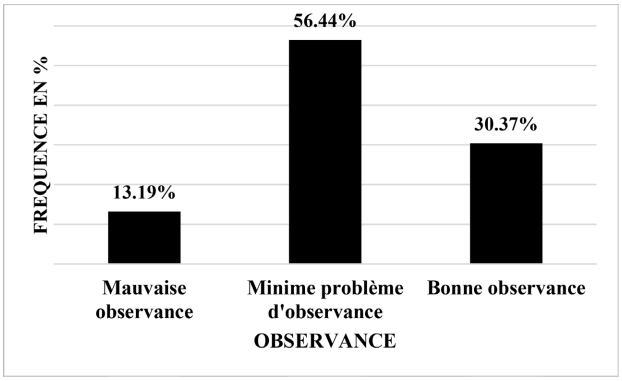
Two hundred and thirteen patients (65.33%) had glycated hemoglobin less than 7%. The mean value of glycated hemoglobin was 6.78% ± 2.22% with extremes of 4% and 19%.

3.7. Control of Other Risk Factors Associated with T2D

One hundred and twenty-eight patients (39.26%) had a normal BMI, 4 were

Table 1. Distribution of patients by diabetes treatment.

MODERN TREATMENT FOLLOWED	NUMBER	PERCENTAGE
Biguanides + Sulfonamides	96	29.45%
Insulin + Biguanides	51	15.64%
Biguanides	51	15.64%
Insulin + DPP-4 inhibitors/Biguanides	50	15.34%
Insulin + Biguanides + Sulfonamides	24	7.36%
DPP-4 inhibitors/Biguanides	14	4.29%
Insulin alone	11	3.37%
Sulfonamides alone	10	3.07%
Exclusive dietetic	10	3.07%
DPP4-inhibitors	3	0.92%
Sulfonamides + DPP4-inhibitors/Biguanides	2	0.61%
Insulin + Sulfonamides	2	0.61%
Sulfonamides + DPP4 inhibitors	1	0.31%
Insulin + DPP4 inhibitors	1	0.31%
TOTAL	**326**	**100.00%**



Mauvaise observance: poor compliance; Minime problème d'observance: minimal compliance problem; Bonne observance: good compliance; Observance: compliance; Fréquence en %: frequency in %.

Figure 3. Adherence to diabetes treatment.

underweight, 117 were overweight. Sixty-seven patients were still moderately obese and 2 were morbidly obese. Obesity was found in 25% of women and 10.4% of men ($p = 0.01$). Abdominal obesity was observed in 151 patients, a prevalence of 47.48% of which 139 were female and 12 male ($p = 0.001$) (Table 2). The average body mass index of our patients was 26.66 ± 4.76 kg/m^2, with extremes of 14.98 and 45.2 kg/m^2.

Hypertension was associated with T2D in 168 patients, a prevalence of 51.53%. These diabetic-hypertensive patients were divided into 124 female and

44 male (p = 0.90). All hypertensive patients were on antihypertensive treatment. Fourteen of the hypertensive patients had a controlled BP (< 130/80 mm Hg) or a control rate of 8.33%.

Dyslipidemia was observed in 183 patients (56.13%), of which 136 were women (74%) and 47 were men (26%) (p = 0.50). Pure hypercholesterolemia was the most represented type with 173 patients, or 95%. (Table 3). Of these patients, 169 received statin-based lipid-lowering therapy, and one patient was treated with fibrate. One hundred and nine patients (33.44%) met the recommended LDL-c targets.

The general characteristic of the patients is reported in Table 4.

Table 2. Distribution of patients by BMI.

CLASSIFICATION BMI	NUMBER	PERCENTAGE
Thinness	4	1.26%
Normal	128	40.25%
Overweight	117	36.79%
Obesity	67	21.07%
Morbid obesity	2	0.63%
TOTAL	**318**	**100.00%**

BMI: body mass index.

Table 3. Distribution of patients by type of dyslipidemia.

TYPE OF DYSLIPIDEMIA	NUMBER	PERCENTAGE
Pure hypercholesterolemia	173	95%
Mixed dyslipidemia	7	4%
Hypertriglyceridemia	3	1%
TOTAL	**183**	**100%**

Table 4. General characteristics of patients by risk factors associated with T2D.

Risk factors	Percentage (%)			p-value (by gender)
	Overall population	Women	Men	
Hypertension	51.53	51.67	51.16	0.90
Dyslipidemia	56.13	56.67	54.65	0.50
Obesity	21.16	24.41	9.3	0.01
Abdominal obesity	47.48	57.91	13.95	0.001
Microalbuminuria	33.74	46.52	38.71	0.2
Physical inactivity	24.23	26.67	17.44	0.10
Tobacco	1.23	0.42	3.49	0.02
Alcohol	5.83	2.92	13.95	0.001

4. Discussion

The average age of patients in our work was 58 ± 11 years. This age of diabetic patients is close to that found by Yameogo *et al.* in Dakar which was 58.2 ± 9.2 years [9]. Diop *et al.* and Ndour *et al.* in African studies found slightly younger patients with an average age of 53.2 ± 9.2 years and 52.2 ± 12.4 years respectively [10] [11]. In contrast, Mcfarlane *et al.* in the United States found an average age of 64.5 ± 0.33 years [12] and Charpentier *et al.* in France 62 ± 11 years [13]. Diabetic patients were younger in African studies than in Western studies. This difference could be explained by the higher life expectancy in the West.

In our work, we noted a female predominance with a sex-ratio of 0.35 as found by Yameogo *et al.* with a sex-ratio of 0.3 [9] and Belhadj in Algeria [11]. On the other hand, a meta-analysis of European studies found a male predominance [14]. This female predominance in our study could be explained by the fact that women are the majority of patients attending hospital structures in our context. This hypothesis had already been defended by Yameogo *et al.* in a similar study [9].

The prevalence of obesity in our study was 21.16%. Yameogo *et al.* found a lower prevalence of 9.11% of obese patients while Charpentier *et al.* in France found a higher prevalence of 39% [9] [13].

The prevalence of abdominal obesity was 47.48% with a very significant female predominance ($p = 0.001$) in our work. This state of affairs could find its explanation at the socio-cultural level, given that African black societies seem to generally encourage overweight among women, being seen as an aesthetic criterion or sign of social comfort. Abdominal obesity is associated with increased metabolic and cardiovascular morbidity and mortality; it leads to a greater sensitivity of perivisceral fat to the lipolytic action of catecholamines, sympathetic nervous system and cortisol, causing an increase in the release of free fatty acids leading to insulin resistance and therefore predisposition to diabetes.

Just under a quarter of patients in our work remained sedentary (24.23%); without any significant difference between the two sexes. In his series, Yameogo *et al.* found that four out of five patients were sedentary [9]. Mbaye *et al.* also found a prevalence of 79.7% of physical inactivity among diabetics in their series [11].

The relatively low sedentary level in our study contrasts with levels obtained in other studies across the country. This could be explained by the fact that our study, being carried out in a center dedicated to cardio-metabolic diseases, the management of patients is much more specialized.

However, the still high rate of inactivity could be explained by the advanced age of the patients, the prevalence of obesity and overweight as well as the female predominance. Indeed, these conditions are often factors limiting the practice of physical activity.

Regular physical activity was identified in the INTERHEART study as one of three factors that reduce the risk of myocardial infarction (the other two being:

regular fruit and vegetable consumption and moderate alcohol consumption) [15]. The cardiovascular benefit of regular physical activity, especially in type 2 diabetics, would come from a significant decrease in peripheral insulin resistance, resulting in a decrease in fasting blood sugar. It also remains beneficial in lowering blood pressure by lowering peripheral vascular resistance.

In our series, tobacco consumption was found in 2 patients (0.6%). This rate was lower than that of 6% found by Yameogo [9]. Charpentier and Belhadj reported prevalence close to 11% and 10% of smokers in their populations, respectively [13] [16]. In McFarlane *et al.*, 17% of men and 7% of women were smokers [12]. The INTERHEART study found that smoking was the second risk factor for myocardial infarction after dyslipidemia [15]. Therefore, its management suggests special attention and patients will have to be accompanied as necessary by supportive psychotherapy for the termination.

A duration of evolution of more than 10 years is found in more than one third of our patients of our work (39.26%) as by several other authors [9] [13] reflecting the chronic nature of this condition.

One-third of our study population (30.37%) had good adherence and just over half had minimal adherence problems (56.44%). Only 13.19% had poor adherence. The reasons for this poor adherence were dominated by poor understanding of treatment followed by fear of addiction or addiction. Low monthly income was a significant cause of poor adherence. The compliance level of our study population was higher than that found by Yameogo *et al.* [9]. Tieno and Abobo *et al.* had found optimal adherence in Burkina in 46.8% and 45% of patients respectively [17] [18].

In the light of these data on anti-diabetic treatment, it is clear that therapeutic education efforts remain to be made to improve patient compliance.

If we consider a glycated hemoglobin target < 7%, 213 patients (65.34%) were controlled. This control rate was higher than the 28.8% found by Yaméogo *et al.* [9] and the 26.7% found by McFarlane [12]. Belhadj *et al.* in Algeria found control rates even lower at 18.7% [16]. The relatively low sedentary rate of our population may have contributed to this. Moreover, the rate of prescription of insulin therapy (42.6%) in line with the duration of diabetes in our series contrasts with the therapeutic inertia often observed in studies of sub-countries developed in relation to the low availability and accessibility of insulin associated with a fear of hypoglycemia [1].

The prevalence of hypertension was 51.53% in T2D in our study with a control rate of 8.33%. A control rate of hypertension slightly higher than that of 5.4% found by Yaméogo *et al.* and lower than the rates of 22% found by Sayad *et al.* [19] 26.5% found by McFarlane in the USA [12]. It appears that blood pressure control is still very insufficient in hypertensive diabetic patients. In diabetics, dual therapy or triple therapy is recommended.

With respect to cholesterol control, 109 patients (33.44%) had achieved LDL-c targets. This rate was close to 35.5% found by Mcfarlane *et al.* [12] and was

higher than the 4% reported by Yameogo *et al.* [9].

5. Conclusion

Type 2 diabetes was frequently associated with other cardiovascular risk factors. Control of diabetes and these factors was insufficient. Therapeutic education of type 2 diabetics patients adapted to our socio-cultural realities needed to be improved. It would also be relevant to carry out longitudinal follow-up of these patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Nations Unies (2022) L'Afrique est la première région du monde pour le diabète non diagnostiqué, selon l'OMS. https://news.un.org/fr/story/2022/11/1129822#

[2] Agence nationale de la démographie et de la statistique du Sénégal. https://www.ansd.sn/sites/default/files/2022-11/1-SES-2017-2018_Etat-structure-population_0.pdf

[3] Mondial, B. (2021) Nouvelle classification des pays en fonction de leur revenu 2020-2021. https://blogs.worldbank.org/fr/opendata/nouvelle-classification-des-pays-en-fonction-de-leur-revenu-2020-2021

[4] Carre, F. (2007) Activité physique et prévention cardio-vasculaire. Cardiologie et maladies vasculaires. Société Française de Cardiologie. Masson, Paris, 4, 302-309.

[5] Consultation OMS sur l'obésité (2003) Obésité: Prévention et prise en charge de l'épidémie mondiale: Rapport d'une consultation de l'OMS. OMS, Série de rapports techniques. Genève. 894. http://apps.who.int/iris/bitstream/10665/42734/1/WHO_TRS_894_fre.pdf

[6] World Health Organization, International Society of Hypertension (1999) Guidelines for the Management of Hypertension. *Journal Hypertension*, **17**, 151-183. https://doi.org/10.1097/00004872-199917020-00001

[7] Cosentino, F., Grant, P.J., Aboyans, V., *et al.* (2020) 2019 ESC Guidelines on Diabetes, Pre-Diabetes, and Cardiovascular Diseases Developed in Collaboration with the EASD. *European Heart Journal*, **41**, 255-323.

[8] Group IDFW (2017) IDF Clinical Practice Recommendations for Managing Type 2 Diabetes in Primary Care International Diabetes Federation—2017. http://www.idf.org/managing-type2-diabetes.IDF

[9] Yaméogo, N.V., Mbaye, A., Ndour, M., *et al.* (2012) Contrôle du risque cardio-vasculaire chez les diabétiques de type 2 noirs africains au Sénégal. *Cardiovascular Journal of Africa*, **23**, 270-272. https://doi.org/10.5830/CVJA-2011-040

[10] Diop, S.N., Wade, A., Lokrou, A., *et al.* (2013) Management of Type 2 Diabetes in Clinical Practices in Sub-Saharan Africa: Results of the AMAR-AFO Study in Senegal and Ivory Cost. *Médecine des Maladies Métaboliques*, **7**, 363-367. https://doi.org/10.1016/S0168-8227(14)70205-0

[11] Ndour Mbaye, M., Sarr, A., Diop, S.N., *et al.* (2011) Diab Care Sénégal: Une enquête sur la prise en charge du diabète au Sénégal. *Médecine des Maladies Métaboliques*,

5, 85-89. https://doi.org/10.1016/S1957-2557(11)70200-0

[12] McFarlane, S.I., Jacober, S.J., Winer, N., *et al.* (2002) Control of Cardiovascular Risk Factors in Patients with Diabetes and Hypertension at Urban Academic Medical Centers. *Diabetes Care*, **25**, 718-723. https://doi.org/10.2337/diacare.25.4.718

[13] Charpentier, G., Genès, N., Vaur, L., *et al.* (2003) Control of Diabetes and Cardiovascular Risk Factors in Patients with Type 2 Diabetes: A Nationwide French Survey. *Diabetes & Metabolism*, **29**, 152-158. https://doi.org/10.1016/S1262-3636(07)70022-8

[14] Ray, K.K., Seshasai, S.R.K., Wijesuriya, S., *et al.* (2009) Effect of Intensive Control of Glucose on Cardiovascular Outcomes and Death in Patients with Diabetes Mellitus: A Meta-Analysis of Randomised Controlled Trials. *The Lancet*, **373**, 1765-1772. https://doi.org/10.1016/S0140-6736(09)60697-8

[15] Yusuf, P.S., Hawken, S., Ôunpuu, S., *et al.* (2004) Effect of Potentially Modifiable Risk Factors Associated with Myocardial Infarction in 52 Countries (the INTERHEART Study): Case-Control Study. *The Lancet*, **364**, 937-952. https://doi.org/10.1016/S0140-6736(04)17018-9

[16] Belhadj, M., Malek, R., Boudiba, A., *et al.* (2010) DiabCare Algérie: DiabCare Algeria. *Médecine des Maladies Métaboliques*, **4**, 88-92. https://doi.org/10.1016/S1957-2557(10)70020-1

[17] Tiéno, H., Bouda, M., Ouédraogo, D.D., *et al.* (2010) Observance to Antidiabetic Treatment in a Developing Country: The Case in Burkina Faso (Sub-Saharan Africa). *Médecine des Maladies Métaboliques*, **4**, 207-211. https://doi.org/10.1016/S1957-2557(10)70046-8

[18] Abodo, J., Oka, F., Ankotché, A., *et al.* (2013) Mesure de l'observance therapeutique chez les patients diabetiques suivis a l'hopital militaire d'Abidjan. *Guinée Médicale*, No. 81, 4-9.

[19] Oulad Sayad, N., Bertal Filali, K. and Diouri, A. (2009) Profil cardio-vasculaire des diabétiques de l'hôpital de jour du CHU Mohammed VI: A propos de 80 cas. *Diabetes & Metabolism*, **35**, 43. https://doi.org/10.1016/S1262-3636(09)71861-0