Scientific Research Publishing

Open Journal of Endocrine and Metabolic Diseases, 2024, 14, 123-134
https://www.scirp.org/journal/ojemd
ISSN Online: 2165-7432
ISSN Print: 2165-7424

Hyperhomocysteinemia and Associated Biological Markers in a Congolese Population of Type 2 Diabetes Mellitus in Brazzaville

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How to cite this paper: Ikia Monde, V.R., Boumba, A.L.M., Mokondjimobe, E., Poaty, H., Loubano-Voumbi, G., Ondongo, W.F., Mayindou Kimbangu, A.G., Onanga, K., Elilie Mawa Ongoth, F., Bouenizabila, E., Andres, C. and Monabeka, H.G. (2024) Hyperhomocysteinemia and Associated Biological Markers in a Congolese Population of Type 2 Diabetes Mellitus in Brazzaville. *Open Journal of Endocrine and Metabolic Diseases*, **14**, 123-134.
https://doi.org/10.4236/ojemd.2024.146015

Received: May 3, 2024
Accepted: June 25, 2024
Published: June 28, 2024

Abstract

The search for new biomarkers predictive of type 2 diabetes currently constitutes a research avenue in Bioclinical. Total homocysteine remains a preferred target due to its involvement in the occurrence of degenerative complications in type 2 diabetics. The aim of this work was to study hyperhomocysteinemia and other biochemical markers associated with T2D in the Congolese population. This was an analytical case-control study carried out between October 2022 and October 2023. The study population consisted of 150 subjects including 100 T2D patients and 50 control subjects. The main clinical data were collected on a pre-established form. Homocysteine determination was carried out by the sandwich ELISA method. The other biochemical markers were measured by colorimetric enzymatic methods. Hyperhomocysteinemia was present in 27.3% (41/150) of the entire study population. Type 2 diabetics had a frequency of hyperhomocysteinemia of 36% (36/100) and control 10% (5/50) (p = 0.001). The mean hyperhomocysteinemia concentration was 31.9 µmol/l with extremes ranging from 18 to 103 µmol/l. Means of biological markers between diabetics and controls showed a statistically significant difference (p = 0.01). The risk factors associated with this HHcy were: sex (OR = 3.5), age (OR = 9.4), sedentary lifestyle (OR = 3.4) and gly-

cosylated hemoglobin (OR = 12) with a p-value <0.05 respectively. Our results suggest that hyperhomocysteinemia can be considered as a predictive biomarker in the bioclinic of Congolese type 2 diabetic patients.

Keywords

Hyperhomocysteinemia, Biological Markers, T2DM, Brazzaville

1. Introduction

Type 2 diabetes (T2DM) represents 80 to 90% of diabetes observed worldwide [1].

In Africa, it affects 22% of the population [1]. In Congo, its incidence is 10% [2].

T2D remains a major public health problem worldwide with clinical consequences leading to chronic multiorgan complications [3].

Alongside the traditional biomarkers of T2DM such as hyperglycemia, high concentrations of glycated hemoglobin (HbA1c), hyperinsulinaemia, hypercholesterolemia, hypertriglyceridemia [4], the search for new biomarkers constitutes a current avenue. in order to improve the prediction and management of T2DM [5].

To this end, total homocysteine (Hcy) has attracted significant scientific interest in recent years. Hcy is a sulfur-containing amino acid, biosynthesized from methionine, the metabolism of which gives it a molecule at the crossroads of two metabolic pathways: trans-sulfuration and remethylation [6].

Hyperhomocysteinemia (HHcy) can have a primary etiology including genetic defects in Methylene Tetra Hydro Folate Reductase (MTHFR) activity and cystathionine b synthase (CBS) deficiency, or acquired through vitamin deficiencies, drug interactions or hypothyroidism [6].

The work of McCully in 1969 demonstrated that HHcy was responsible for atherothrombotic pathologies [6]. Since then, several studies have been conducted on the association between HHcy levels and T2DM as well as the occurrence of these vascular complications. It appears that HHcy was correlated with insulin resistance [7], dyslipidemia and poor control of T2DM [8]. Also, HHcy would lead to a worsening of T2DM by induction of reversible dysfunction of β-islet cells and inhibition of insulin secretion [9].

Despite these scientific advances, the mechanisms of interaction between plasma HHcy levels and T2DM as well as the aggravating factors have not yet been completely elucidated. Recent studies investigating these mechanisms present contradictory results [7] [8] [9] [10].

Thus, the evaluation of Hcy, little explored in sub-Saharan Africa, remains a privileged target due to its involvement in the occurrence of degenerative complications of T2DM [11] [12] [13].

The objective of this work was to study the prevalence of HHcy and its association with bioclinical characteristics in a Congolese population of type 2 diabetics.

2. Patients and Methods

This was a prospective, analytical study carried out over a period of twelve months (October 2022 to October 2023 at the University Hospital Center of Brazzaville and in collaboration.

Patient recruitment was carried out at the DIABC@RE center and in the endocrinology department of the University Hospital Center of Brazzaville (CHU-B) and at the Faculty of Health Sciences (FSSA) of Marien Ngouabi University.

2.1. Patients

The study included 150 individuals including 100 known type 2 diabetics and 50 controls (healthy, non-diabetic subjects composed of healthcare staff, students and volunteers).

The diabetics were divided into three subgroups: G1, composed of 34 cases with macrovascular and microvascular complications; G2, containing 33 cases with comorbidities; G3, bringing together 33 non-carrier cases without comorbidities or complications.

Patients treated with Metformin were not included in our study. All patients with a pathology that could influence Hcy concentration, such as renal failure, liver disease, hypothyroidism and cancer, were excluded.

2.2. Methods

2.2.1. Epidemiological and Clinical Investigations

The information and the different variables considered were transcribed onto a pre-established sheet. These are: family history of diabetes mellitus, high blood pressure, obesity and hyperlipidemia, anthropometric data (weight, height, BMI,) and sociodemographic data (age, sex, smoking, sedentary lifestyle).

2.2.2. Biochemical Analyses

5ml of venous blood was taken after a 12-hour fast, in a tube containing sodium fluoride for measuring blood sugar, and in a dry tube for renal assessment (creatinine, urea) and lipid assessment (total cholesterol). triglycerides, HDL cholesterol, LDL cholesterol). Two tubes containing an EDTA K3 anticoagulant were used for the determination of HbA1c and Hcy.

After processing and packaging, the samples were sent to the CHU-B biochemistry laboratory for blood sugar measurement, lipid and renal assessment; at the Iris laboratory for the HbA1c assay and at the FSSA Training, Research and Biomedical Analysis laboratory for the Hcy assay.

The analyses were carried out by 3 types of methods:

- Tringer (on Abbot ARCHITECT C4000r): colorimetric and enzymatic method made it possible to perform blood sugar, renal and lipid assessment in search of associated complications;

- Fluorescence immunochromatography (on iCHROMA II): for the determination of HbA1c;

- "micro-fluidic" immunochromatography of sandwich ELISA type (on PHOMO) for Hcy dosage.

3. Statistical Analyses

All data were analyzed by SPSS® software (version 20.0). Multivariate analysis was used to study the association between HHcy and other variables. Statistical analyses were carried out with a 95% confidence interval and a significant p value < 0.05.

4. Results

4.1. Epidemiological Data

4.1.1. Age

The distribution of mean age between diabetic subjects and controls (Figure 1) was 52.2±10.8 years in T2D patients, with extremes ranging from 30 to 83 years. The controls had a mean age of 42.3 ± 7.1 years, with extremes of 28 to 61 years (p = 0.000).

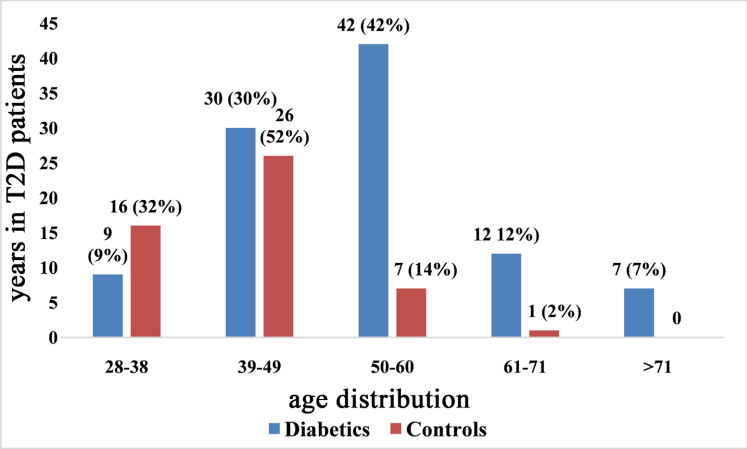


Figure 1. Age distribution according to diabetic subjects and controls.

4.1.2. Sex

T2D was diagnosed in both women and men with a sex ratio of 1 (50% men and 50% women). Among controls, the sex ratio was 0.44 (36 women, 72% and 16 men, 28%) (p = 0.01).

4.2. Biological data

Table 1 presents the main results of routine assessment and Hcy in T2D patients and controls. An HHcy was observed with an average of 19.16 µmol/l.

Table 1. Mean values of biochemical analyses in the 2 study groups.

Biochemical biomarkers	Common values	Mean ± Standard deviation		p-value
		Diabetics	Control	
Plasma glucose (mmol/l)	3.85 - 6.60	10.78 ± 0.55	5.06 ± 0.18	0.000
SerumCreatinine (µmol/l)	61.8 - 123.7	111.82 ± 4.57	95.55 ± 1.97	0.001
Urea (g/l)	0.15 - 0.45	0.277	0.19	0.003
Total Cholesterol (g/l)	1.4 - 2.0	1.55 ± 0.34	1.29 ± 0.1	0.000
HDL Cholesterol (g/l)	> 0.60	0.35 ± 0.05	0.32 ± 0.04	0.001
LDL Cholesterol (g/l)	0.4 - 1.3	0.94 ± 0.32	0.76 ± 0.11	0.000
Triglyceride (g/l)	0.4 - 1.65	1.16 ± 0.41	0.99 ± 0.13	0.000
HbA1c (%)	<6	8.92 ± 2.3	4.44 ± 0.91	0.000
Homocysteine (µmol/l)	5 - 15	19.16 ± 15.27	6.28 ± 2.08	0.000

4.3. Frequency of Hcy and HHcy

The analysis of Hcy in the two study groups was reported in Table 2. Hcy was normal in 64% (64/100) of T2DM compared to 90% (45/50) of controls with averages of 19.16 µmol/l and 6.18 µmol/l respectively in the diabetic and control groups.

Table 2. Expression of Hcy and HHcy levels in the 2 study groups.

Judgment criteria		Intervals (µmol/l)	Diabetics		Controls	
			n	%	n	%
Normal Hcy		<15	64	64	45	90
HHcy	Moderate	15-30	20	20	5	10
	Intermediate	31-100	15	15	0	0
	Severe	>100	1	1	0	0
Total		100	100	100	50	100

Thus, HHcy was presented according to the different HHcy levels (Moderate: 15 - 30 µmol/l; Intermediate: 30 - 100 µmol/l and Severe: >100 µmol/l) [14]. Indeed, 36% (n = 36) of T2DM had HHcy of which 20% (n = 20) of patients had moderate HHcy, 15% (n = 15) intermediate HHcy and 1% (n = 1) HHcy severe. In the control group, moderate HHcy affected 10% of cases (n = 5).

4.4. Hyperhomocysteinemia in Diabetics

Table 3 distributes the Hcy and HHcy levels according to the three subgroups of diabetics.

Table 3. Distribution of HHcy in type 2 diabetics.

Subgroups	HHcy (µmol/l)			Total (%)
	Moderate (15 - 30)	Intermediate (31 - 100)	Severe (>100)	
G1: With comorbidities	16.7	2.7	0	19.4
G2: With complications	16.7	39	2.7	58.4
G3: Without comorbidities or complications	22.2	0	0	22.2
Total (%)	55.6	41.7	2.7	100

HHcy was found in 36% (36/100) of T2D patients, with a mean concentration of 33.3 µmol/l and ranges from 18 to 103 µmol/l. This HHcy was found in (i) 19.4% of patients in G1 including 16.7% with moderate HHcy, 2.7% intermediate, (ii) 58.4% in G2 or 16.7% with moderate HHcy, 39% intermediate and 2.7% severe. (iii) As for G3, 22.2% had moderate HHcy.

4.5. Factors Associated with HHcy

Table 4 presents the factors associated with HHcy including sex (OR = 3.5; p = 0.003), age (OR = 9.4; p = 0.000), sedentary lifestyle (OR = 3; p = 0.029) and the glycated hemoglobin level (OR = 12.7; p = 0.002).

Table 4. Factors associated with HHcy in T2DM.

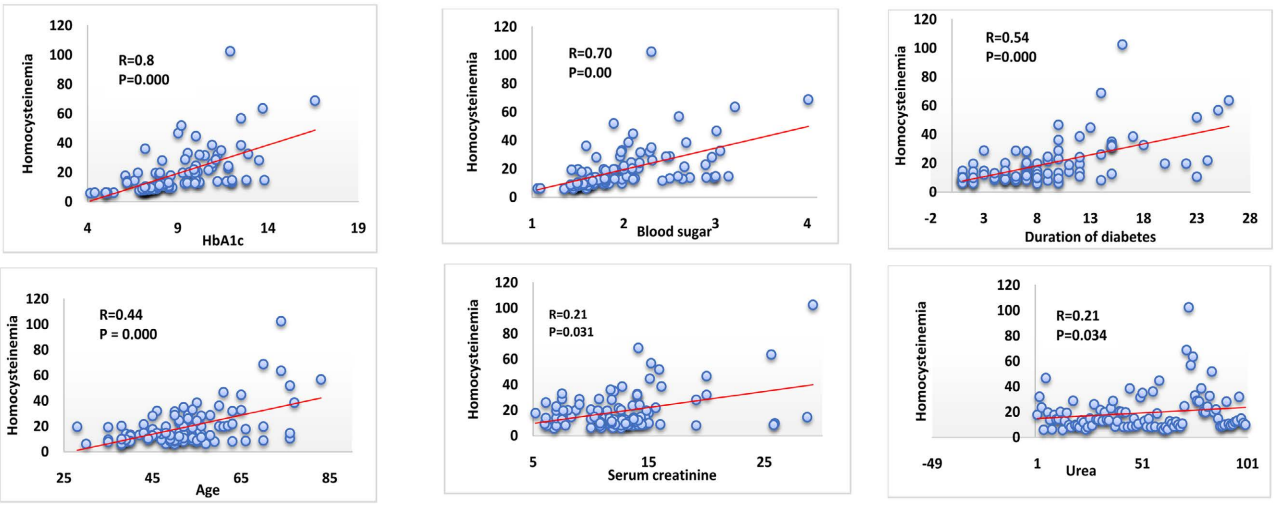
		HHcy		OR	IC à 95%	p-value
		Yes	No			
Variables						
Sex	Man	25	25	3.5	1.5 - 8.4	0.003
	Woman	11	39			
Age (year)	>60	16	5	9.4	3.1 - 29.1	0.000
	<60	20	59			
BMI (kg/m^2)	<25	7	24	0.4	0.1 - 1.1	0.0609
	[25 - 30]	25	34			
	>30	4	6	1.2	0.3 - 4.6	0.7811
Sedentary	Yes	30	40	3	1.1 - 8.3	0.0291
	No	6	24			
Biomarkers						
Total cholesterol (g/l)	>2	5	6	1.5	0.4 - 5.5	0.4886
	[1.4 - 2]	31	58			
Triglyceride (g/l)	>1.65	9	14	1.2	0.4 - 3.1	0.7215
	<1.65	27	50			

Continued

Serum creatinine (mg/l)	>14	14	15	2.1	0.9 - 5	0.1021
	<14	22	49			
Urea	<0.15	0	1	-	-	
	[0.15 - 0.45]	32	60	0.5	0.1 - 2.3	0.3897
	>0.45	4	3	1.9	0.4 - 7.9	0.2268
LDL cholesterol	<0.4	1	2	0.9	0.1 - 10.1	0.9221
	[0.4 - 1.3]	28	54	0.6	0.2 - 1.8	0.4098
	>1.3	7	8	1.7	0.6 - 5.1	0.3505
HDL cholesterol	<0.35	0	0	-	-	
	[0.35 - 0.65]	18	30	1.1	0.5 - 2.7	0.7639
	> 0.65	18	34	0.9	0.4 - 1.9	
Blood sugar (g/l)	≥ 1.25	36	57	-	-	0.0396
	[1 - 1.25]	0	7			
HbA1c (%)	≥7	35	47	12.7	1.6 - 99.7	0.0029
	<7	1	17			

4.6. Correlations between Hyperhomocysteinemia and Other Biomarkers and Variables

Figures 2 present the different existing correlations between HHcy and other biomarkers and other variables. Indeed, strong correlations were found between HHcy and HbA1c (R = 0.8) as well as Blood Glucose (R = 0.783). They were moderate between HHcy and duration of diabetes (R = 0.54l) as well as with age (R = 0.44): $p < 0.000$. However, HHcy was weakly correlated with serum creatinine (R = 0.21) and urea (R = 0.213): $p > 0.05$.



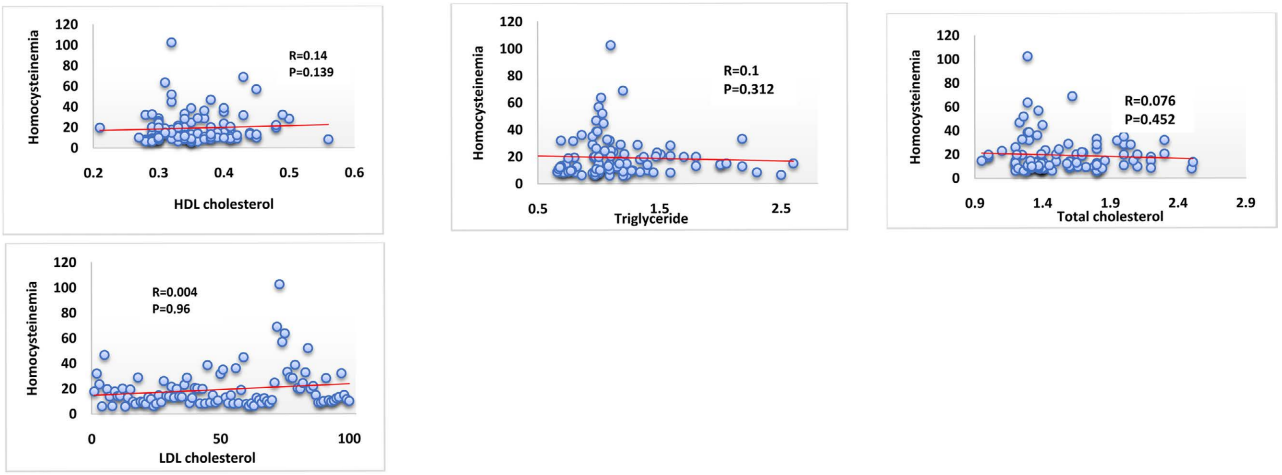


Figure 2. Spearman correlations obtained between homocysteinemia and the different biochemical biomarkers.

5. Discussion

Diabetes mellitus is a rapidly growing disease, particularly T2DM which is the most common form of the disease. It is associated with high cardiovascular morbidity and mortality. Several cardiovascular risk factors and markers exist, including HHcy. Our study aimed to determine the prevalence of HHcy in the Congolese type 2 diabetic population at CHU-B, to explore and verify its possible association with bioclinical characteristics. This is with the aim of evaluating the interest in determining this molecule in the monitoring and prevention of degenerative complications of T2DM, which is a current issue.

The results of biochemical biomarkers between T2DM patients and controls were statistically significant ($p < 0.05$). Lipid and renal biomarkers have variation kinetics consistent with T2DM imbalance ($p < 0.05$). As for the diagnostic and monitoring markers such as blood sugar and HbA1c, their values also conform to the kinetics of the metabolic imbalance caused by T2DM [15]. This metabolic imbalance was found in our study as evidenced by the high HbA1c levels (OR = 17.5) in our T2DM patients which could be the consequence of poor monitoring control probably generating the high value of the Hcy.

The results of this work revealed that HHcy was found in 27.3% of patients in the entire population studied, i.e. 36% in T2DM and only 10% in controls. This prevalence varies in studies carried out in different areas of Africa. Indeed, in West Africa, Mabchour and colleagues reported a prevalence of HHcy of 38.5% in Benin [11], while in Togo, the work carried out by Amouzou *et al.* [16] reported a 56% prevalence of HHcy in the general population.

Work carried out among T2DM in North Africa reports higher prevalences of 38.8% in Morocco [17] and 62.9% in Algeria [10] while in a Tunisian population study, Lakhoua *et al.* reported a prevalence lower than ours of 23% [18].

Studies carried out in Europe in a French and Italian country have successively reported prevalences of 9% [19] and 40% [20].

Our results are consistent with certain studies having observed a strong correlation between moderate HHcy and T2DM, in Ivory Coast and Mali, respectively

73.7% and 61% [21] [22]. The level of moderate HHcy that we found in our series (61% of cases) is higher than that reported by Chadli in Tunisia (47.5%) [23] and in Togo 44.8% [24].

In T2DM, the known cardiovascular risk factors are: obesity, high blood pressure, dyslipidemia, and smoking. However, other risk factors, less frequently taken into account, may intervene, in particular HHcy. Intervention studies seem to show that HHcy could be considered a cardiovascular risk factor in type 2 diabetics [11] [17].

The HHcy observed in our study and other studies cannot be the only consequence of dysglycemia, but it can also be linked to the influence of FDR associated with T2DM.

The increasing increase in the average concentration of Hcy with age has been found in numerous studies [22] [25]. Indeed, in our series, we noted that the average age of patients with HHcy was 49.3 years. Subjects over 49 years old only represented 46% of the total number of our study and the age group most affected in HHcy was that of 50 - 60 years old (n = 18) i.e. 43.9% followed by that of 61 - 71 years old (n = 10) or 24.4%, while the age group of 39 - 49 years represented only 12.2% (n = 5). We observed and confirmed a correlation between complications (stroke and hypertension) and HHcy in the proportion of T2DM patients around 49 years of age. In the literature, it is established that Hcy increases over the years between the ages of 20 and 70 [26].

The consistency of increase in Hcy with risk factors could be explained by the mechanism of physiological deterioration of renal function [27], gastric atrophy and an inadequate diet of vitamins and folates, observed in elderly subjects [26].

Sex is also one of the factors that can influence Hcy concentrations. Our work revealed an average HHcy concentration higher of 68.8% in men and 34.1% in women. Our results are similar to similar studies carried out in Africa reporting HHcy concentrations of 52.2% and 52.6% respectively in Beninese and Ivorian men [11] [21]. Some data from the literature confirm this trend of increase in this biomarker in men compared to women [8] [13] [26].

Numerous studies have shown that HHcy appears to be a greater FDR in T2DM patients than in non-diabetic subjects [5] [8]. In our study, HHcy was observed more in T2DM than in controls. They represented 58.4% of patients with degenerative complications of T2DM. Indeed, the imbalance of diabetes and the status of degenerative complications of T2DM gave HHcy a particular profile of increasing cardiovascular risk. This suggests that HHcy could be a predictive marker of degenerative complications in T2DM, alongside other traditional risk factors. Our results are consistent with data from the literature [8] [12] [23]. Other studies, however, have not shown a significant difference between the two groups [28].

Strong correlations were found between HHcy and HbA1c (R = 0.8) as well as blood sugar (R = 0.783). The HHcy was also moderately correlated with the duration of diabetes (R = 0.54l and age (R = 0.44). Some data from the litera-

ture corroborate our results [5] [17]. Also, the Hcy was weakly correlated with serum creatinine (R = 0.21) and urea (R = 0.213). Our results are in agreement with the literature [25]. However, studies [5] [17] [26] have highlighted evidence of a strong correlation between Hcy and total cholesterol which was not observed in our result. Likewise, no correlation between HHcy and triglycerides was found in our work. This was a source of divergence in numerous studies [5] [29] [30].

These results confirm the dependence between diabetes control and Hcy concentrations.

This work raises the question of HHcy as a predictive factor, isolated or associated with other risk factors and biological markers, of the occurrence of degenerative complications of T2DM. Also, the lack of dosage of folates and cobalamins in the biological assessment can justify this HHcy. Indeed, a multifactorial analysis taking into account nutritional modalities and other missing risk factors would make it possible to highlight explanatory variables. A large multicenter study could make it possible to identify these variables if they exist in the Congolese type 2 diabetic population.

6. Conclusions

The identification of HHcy expression found in this work demonstrated the link between this biomarker and other biological parameters associated with type 2 diabetes.

The glycemic imbalance observed between HHcy and other traditional biological markers is an incentive to measure Hcy in the monitoring of diabetic patients. In addition, correlations have been established between HHcy, HbA1c and serum creatinine.

Thus, homocysteine can be considered as a predictive biomarker in the bioclinical of T2DM.

Acknowledgements

All our thanks go to: CHU-B Biochemistry Laboratory, IRIS Laboratory and the FSSA Training, Research and Biomedical Analysis Laboratory for biochemical analyses; Health Doctoral Training in Human Biology at the Faculty of Health Sciences.

Contribution To Authors

MHG, ME, and AC initiated the project. IMVR and MKGA carried out the experiment. EMOF, BE, MHG enabled patient recruitment. Proofreading of the manuscript by MME and HP, with the contribution of AC, LVG and BALM.

Conflicts of Interest

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

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